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Title sheet

Title: Adverse health outcomes in antidepressants users.

Subtitle: An umbrella review of 45 meta-analyses of observational studies.

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Abstract

Importance: Antidepressant use is increasing worldwide. Contrasting evidence from meta-analyses is available on their safety.

Objective: To grade the evidence across meta-analyses of observational studies assessing the association between antidepressants and adverse health outcomes, using an umbrella review approach.

Data Sources: We searched PubMed, Scopus, and PsycINFO, up to April 5, 2019.

Evidence Review: Only meta-analyses of observational studies with a cohort or case-control study design were eligible. Two independent reviewers recorded the data and assessed the methodological quality of the selected meta-analyses. Evidence was ranked as convincing, highly suggestive, suggestive, weak, and not significant according to established criteria**.**

Results: Forty-five eligible meta-analyses describing 120 associations including data from 1012 individual effect size estimates were included, after scrutinizing 252 potential articles. Seventy-four of the 120 associations (61.7%) had a nominally statistically significant effect ($p \leq 0.05$) using random-effects models. Large heterogeneity ($I^2 > 50\%$) was present (43.3%), while small-study effects (14.2%) and excess significance bias (7.5%) were less common. While convincing meta-analytic evidence emerged from both main and sensitivity analysis for the association between antidepressants and risk of suicide attempt/completion in children/adolescents (9.4%, OR=1.92, 95%CI=1.51-2.44 in adjusted studies, SSRIs only, and in high-quality studies, 3.6% OR=1.88, 95%CI=1.47-2.40), autism spectrum disorders (ASD) with antidepressants before (0.8%, RR=1.48, 95%CI=1.29-1.71 in any antidepressant, adjusted studies, and high-quality studies) and during pregnancy (0.9%, OR=1.84, 95%CI=1.60-2.11 in both high-quality studies and SSRIs only, and 0.1% OR=1.80, 95%CI=1.54-2.10 in European studies), pre-term birth in prospective cohort studies (0.4%, RR=1.87, 95%CI=1.52-2.30), and in studies of mixed antidepressants (0.4%, RR=1.59, 95%CI=1.31-1.93), and low APGAR scores in SSRIs only studies (5.7%, SMD=-0.27, 95%CI -0.37

to -0.16), none of these associations remained at convincing evidence after sensitivity analysis for confounding by indication.

Conclusions and Relevance: Most putative adverse health outcomes associated with antidepressants are not supported by convincing evidence, and the few of those supported by convincing evidence are affected by confounding by indication. Antidepressants appear to be overall safe for the treatment of psychiatric disorders. More studies matching for underlying disease are needed to clarify the degree of confounding by indication and other biases. No absolute contraindication to antidepressants emerges from this umbrella review.

Registration: PROSPERO registration 2018: CRD42018103462.

Key words: antidepressants; adverse outcomes; umbrella review; meta-analysis; safety

Key Points

Question: Are antidepressants associated with adverse health outcomes and how strong is the evidence in the published meta-analyses of real-word data?

Findings: In this systematic umbrella review of 45 meta-analyses of observational studies, convincing evidence was found for the association between antidepressants and suicide behavior/completion in individuals aged <19 years old and for autism risk in the offspring. However, none of these associations remained at convincing evidence after sensitivity analysis for confounding by indication.

Meaning Claimed adverse health outcomes associated with antidepressants are not supported by strong evidence and are exaggerated by confounding by indication. No absolute contraindication to the use of antidepressants is currently supported by convincing evidence.

Introduction

Accumulating evidence suggests that there is a sharp growth of antidepressants use worldwide (up to 8-10% of American adults take at least one antidepressant - rank third among prescribed and fourth among sold medications).[1,2] Antidepressants are indicated and used for depressive disorders, anxiety disorders, post-traumatic stress disorder, premenstrual dysphoric disorder, obsessive compulsive disorder (OCD), binge eating disorder, among others.[3-5]

The safety profile of antidepressants is controversial. Since the Food and Drug Administration (FDA) introduced the black box warnings associating selective serotonin reuptake inhibitors (SSRIs) with an increased risk of suicidal behavior in children and adolescents,[6] the debate about efficacy, acceptability, and the safety profile of antidepressant medications has gradually increased.[7-11] While evidence from randomized controlled trials (RCTs) showing antidepressants' efficacy and acceptability has been well documented, in both meta-analyses and network meta-analyses,[4,8,10,12,13] safety assessment is inherently biased by certain methodological weaknesses of RCTs, such as small and unrepresentative samples, rare and inconsistent reporting of adverse outcomes, and short duration of exposures.[14,15]

Observational studies provide complementary evidence to RCTs on a number of adverse health outcomes (which may only manifest in the mid- to long-term) utilizing real-world data[15] linked to antidepressants, which it is not possible in RCTs.[16] In particular, observational studies can provide useful evidence on medication safety since they are more representative of overall target population, for example including patients with comorbid disorders or suicidal thoughts, which are often excluded from RCTs. Also, observational studies typically have a longer follow up duration than RCTs, providing data on mid- and long-term effects of antidepressants, such as bone status, or gastro-intestinal bleeding which may not arise from short-term use.[16] Several meta-analyses of observational studies assessing antidepressant safety have been published, but no attempt of quantifying their credibility has been made to date. The latter is crucial, considering the uncertainty

surrounding observational research results.[17-19] Umbrella reviews make it feasible to summarize the evidence from multiple meta-analyses on the same topic [20,21] and enable a grading (ranking) of evidence into convincing, highly suggestive, suggestive, weak, or not significant based on sample size, strength of the association, and the assessment of presence of biases.[22-24] In this study, we graded the evidence from published meta-analyses of observational studies testing the association between antidepressant use and risk of adverse health outcomes.

Methods

A protocol for this study was registered on PROSPERO 2018: CRD42018103462. We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations [25] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[26] to guide this umbrella review.

Search strategy and selection criteria

We searched the PubMed, Scopus, and PsycINFO, from inception to April 5, 2019, to identify systematic reviews with meta-analysis of observational studies that examined an association between any adverse health outcome and exposure to antidepressants. We performed a search strategy using a combination of terms related to antidepressants (e.g., ″antidepressants", "selective serotonin reuptake inhibitors"), terms related to adverse health outcomes (e.g., "harms," "suicide," "bleeding," "autism," etc.), and to meta-analysis with no age, sex, population, and medical condition restrictions (for details, see eBox1 in the Supplement). We also hand searched the cited references of the retrieved articles and reviews.

Two reviewers (ED, MS) independently searched titles/abstracts for eligibility, and when a consensus could not be achieved a third reviewer was consulted (EE). The full-texts of potentially eligible articles were retrieved, and the same two investigators independently scrutinized each study for eligibility. Any discrepancies were resolved by the third reviewer (EE).

We included only peer-reviewed systematic reviews with meta-analysis of observational studies with only a cohort, case-control, or nested case-control study design, measuring any association between antidepressants and any adverse health outcome in any population of any age. Whenever multiple meta-analyses on the same adverse health outcome were performed (i.e., overlapping meta-analyses with the same outcome, type of antidepressant, and clinical setting or population setting), we assessed only the one that included the largest data set, as previously described.[22,24,27] Details of the selection between overlapping meta-analyses are described in the Supplement. For each eligible meta-analysis, we considered the main analysis for all primary and secondary reported outcomes. The concordance between selected and non-selected meta-analyses was examined in a sensitivity analysis.[27]

We excluded: 1) meta-analyses of other study designs (e.g., RCTs, cross-sectional) or meta-analysis included both observational studies and RCTs in the same analysis, 2) published in languages other than English, 3) meta-analyses of individual patient or participant data, pooled analyses that examined a non-systematic selection of observational studies, and non-systematic reviews, 4) meta-analyses of hypericum perforatum, known as perforate St John's-wort, or tryptophan, and 5) meta-analyses that provided insufficient or inadequate data for quantitative synthesis.

Data extraction

Data extraction was performed independently by two investigators (ED, MS) and disagreements were resolved by a consensus. Adverse health outcomes related to exposure to antidepressants were extracted as defined by the original authors. For each meta-analysis, we recorded information on PMID/DOI, first author, publication year, type of antidepressant, study design, age of participants, adverse health outcomes, exposure and non-exposure, illnesses examined (e.g., depression), the number of included studies, and the total sample size.

For each primary study, we recorded information on first author, year of publication, study design (i.e., cohort or case-control), number of cases and controls in case-control studies or total population in cohort studies, reported adjusted (or unadjusted, if such exists) effect sizes (ESs), i.e.; risk ratio (RR); odds ratio (OR), hazard ratio (HR), standardized mean difference (SMD), each with their 95% confidence intervals (CIs), and study location. We also captured the number and nature of adjustments, length of follow-up, study quality score, and if the studies were controlled for a psychiatric condition, i.e., confounding by indication.[18,19]

Data were extracted independently by two investigators (ED, MS). The methodological quality of each included meta-analysis was assessed with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at https://amstar.ca/Amstar-2.php), which is a recent update of AMSTAR,[28] by same two investigators (ED, MS). AMSTAR 2 also accounts for the quality of studies included in the meta-analysis, beyond a mere technical methodology assessment of the included meta-analysis (for details see supplement).[16]

Data analysis

For each association, we extracted effect sizes of individual studies included in each meta-analysis, and re-meta-analyzed them calculating the pooled ES and the 95% confidence intervals, with random-effects models to compare homogeneously analyzed results.[29] We did not transform the initial ESs or modify the direction of associations presented by the original authors to compare our results with the reported results from the meta-analyses. Heterogeneity was assessed with the I^2 statistic.[30] Additionally, we calculated the 95% prediction intervals for the summary random ESs providing the possible range in which the ESs of future studies is expected to fall.[31]

We then tested whether smaller studies yielded larger ESs than larger ones; an indication of small-study effect bias.[24,32-34] Small-study effect bias was indicated by both Egger's regression asymmetry test ($p \leq 0.10$) and by the random effects' summary ES being larger than the ES of the largest study in each association.[24,32-34] Finally, we assessed the existence of excess significance bias

by evaluating whether the observed number (O) of studies with nominally statistically significant results ("positive" studies, $p \leq 0.05$) were different from the expected number (E) of studies with statistically significant results.[34] The E of statistically significant studies per association was calculated by summing the statistical power estimates for each component study. The power estimates of each component study depend on the plausible effect size for the tested association, which we assumed to be the effect of the largest study (i.e., the smallest standard error) per association.[35] Excess significance bias was set at $p \leq 0.10$. This test is designed to assess whether the published meta-analyses comprise an over-representation of false positive findings.[34]

Assessment of the credibility of the evidence

We assessed the credibility of the evidence per association provided in meta-analyses by applying several criteria in concordance with previous published umbrella reviews.[22,23,32,33,36,37] In brief, associations that presented nominally significant random-effects summary ESs (i.e., $p \leq 0.05$) were ranked as convincing, highly suggestive, suggestive, and weak evidence based on sample size, strength of the association, and the assessment of presence of biases (Table 1; for details see Supplement). In addition, to provide an estimate of epidemiologic implication of findings, we calculated prevalence of outcomes of interest from cohort studies only (studies with case-control designs should not be considered for prevalence estimates).

Sensitivity analysis

We performed sensitivity analyses to assess whether the credibility of the evidence varied within cohort studies (both prospective and retrospective), prospective cohort studies, studies with adjustments for multiple covariates, confounding by indication, high-quality studies, classes of antidepressants (SSRIs studies, tricyclic antidepressants [TCAs] studies, other or mixed antidepressants studies), and study location of the associations ranked as convincing and highly suggestive (i.e., class I-II) in the main analysis.

Results

We identified 4,471 articles, scrutinized 252 in full text and finally included 45 meta-analyses in this umbrella review [38-81] (Figure 1), corresponding to 695 studies, 1012 estimates, and 13 putative risks (Figure 2). References of the 207 excluded articles and their reasons are provided in eTable 1.

Descriptive characteristics of the 45 eligible meta-analyses of observational studies can be found in eTable2. All meta-analyses but one had also a control group not exposed to antidepressants, in which compared the risk of gastrointestinal (GI) bleeding between mirtazapine and SSRIs.[47] The median number of adjustments in the analyses was 7 (interquartile range [IQR]=4-11, range 0-31) and the median duration of follow-up was 4 years (IQR=2−5).

Thirty-three meta-analyses (73.4%) met the moderate-quality level according to the AMSTAR2 evaluation, and eight (17.8%) were of low quality. Finally, two (4.4%) were high-quality, while two others (4.4%) were of critically low quality. The two independent investigators reached a high level of agreement (91.0%) on the quality rating.

Description of associations

Forty-five eligible meta-analyses described 120 associations including 1012 individual study estimates of adverse health outcomes related to exposure to antidepressants (see Tables 1 to 2, and eTables 3 to 5 in the Supplement), with a median number of estimates per association of 6 (IQR =4-12). Seventy-four (61.7%) of the associations concerned maternal and pregnancy-related adverse health outcomes (Figure 2). Most associations (n=80; 66.7%) concerned SSRIs or SNRIs, nine (7.5%) TCAs, and 31 (25.7%) mixed or other antidepressants.

The median number of the total population per association was 1,056,374 (IQR=152,180 – 2,215,969). The median number of cases (adverse health outcomes) per association was 12,097 (IQR=2,585−56,272) and the number of cases was >1,000 for 87 associations (72.5%).

Summary of associations

A summary of all 120 associations is presented in Tables 2 to 3 and eTables 3 to 5 in the Supplement. Seventy-four of the 120 examined associations (61.7%) had a nominally statistically

significant effect ($p \leq 0.05$) using random-effects models and only 22 of those (18.3%) reached $p \leq 1x10^{-6}$.Almost all statistically significant associations indicated an increased risk for antidepressants and adverse health outcomes, except for two associations showing a protective effect of SSRI against suicide attempt/completion in adults and older adults, respectively.[80]

Fifty-two associations (43.3%) had large heterogeneity (I2>50%), and only for 24 associations (20.0%) the 95% prediction intervals excluded the null value. In 63 associations (52.5%), the ESs of the largest study presented a nominally statistically significant effect ($p \leq 0.05$). Finally, small-study effects were found for 17 associations (14.2%), and excess significance bias was observed for nine associations (7.5%).

Grading of level of evidence of associations

Main analysis

Convincing evidence

Among the 120 associations, three (2.5%) had convincing evidence; the association between SSRIs and increased risk of suicide attempt/completion in children and adolescents,[80] and the association between any antidepressant before pregnancy and SSRIs during pregnancy and autism spectrum disorders (ASD)[51,52] (Table 2). The association with suicide risk reached high-quality level based on AMSTAR2, while the two associations with ASD reached moderate quality.

Highly suggestive evidence

For 11 associations (9.2%), there was highly suggestive evidence for the relationship between any antidepressant and increased risk of adverse health outcomes (Table 2), namely attention-deficit hyperactivity disorder (ADHD) in children, cataract development (TCAs), severe bleeding at any site, upper GI bleeding, postpartum hemorrhage, preterm birth, lower APGAR score at 5 minutes, osteoporotic fractures (one for TCAs and one for SSRIs), and risk of hip fracture. Seven of these associations reached moderate quality level based on AMSTAR2 (Table 2). One association with

highly suggestive evidence, however, showed a decreased risk (i.e., protective association) of suicide attempt/completion in adults,[80] meeting a high-quality level based on AMSTAR2.

Suggestive, weak, and no evidence

There was suggestive evidence for 21 further associations (17.5%) linked to increased risk of adverse health outcomes (eTable 3). For the remaining associations, there was either weak (n=39 [32.5%]) or no evidence (n=46 [38.3%]; all associations with p>0.05) (eTables 4 and 5).

Sensitivity analyses

A sensitivity analysis limited to cohort studies, prospective cohort studies, studies controlled for confounding by indication, and North American studies showed that none of the associations within convincing evidence (class I) retained the same rank (Table 3).The most important change was within prospective cohort studies, with one being upgraded to convincing evidence (preterm birth related to any antidepressant).

Another association was upgraded to convincing evidence (lower APGAR scores at 5 minutes) when the sensitivity analysis was limited to SSRIs, as well as the association with preterm birth was also upgraded to convincing evidence when the analysis was limited to other or mixed antidepressants (Table 3).

A further sensitivity analysis limited to non-selected meta-analyses due to overlap agreed with the results of the main analysis (Supplement results and eTable 6). The results of each sensitivity analysis are presented in detail in the Supplement with the full list of covariates in eTable 7.

Discussion

We reviewed 45 meta-analyses of observational studies and we found that only a few of the 74 statistically significant associations between antidepressants and adverse health outcomes had convincing evidence in main and sensitivity analysis, namely the association between antidepressants and increased suicide behavior/completion in individuals aged <19 years old (SSRI),[80] autism risk in the offspring,[51,52] preterm birth,[66] and neonatal adaptation.[71] However, the few convincing

associations do not reflect necessarily causality and, importantly, none of them remained at convincing evidence after accounting for confounding by indication. Overall, our results show that the association between antidepressants and adverse health outcomes is not supported by robust evidence and the underlying disease likely affects the results and inflates significant findings in a relevant way.[39,44]

To our knowledge, this is the first umbrella review that systematically assesses the potential risk of adverse health outcomes related to antidepressants across a large spectrum of published meta-analyses of observational studies, grading also the evidence by applying well-recognized criteria of its credibility. [22,23,32,33,36,37] This umbrella review approach has been previously applied to other fields of medicine, such as adverse health outcomes of dietary fiber consumption,[37] serum uric acid,[23] and vitamin D.[22] Our approach fits to a research field that is undeniably complex and uncertain, as conveyed here. [22,23,32,33,36,37] The large median number of participants and cases per association allowed to make robust classifications; the number of cases was greater than 1,000 for 87 out of the total of 120 associations. Quality ratings of the included meta-analyses with the AMSTAR2 tool also allowed to interpret our results with confidence. Sensitivity analyses provided additional evidence from cohort, high-quality studies, and studies that were controlled for a psychiatric condition, further increasing reliability of the results.

Our results need to be considered when contemplating the use of antidepressants in children/adolescents integrating this knowledge with data on efficacy from RCTs. A network meta-analysis of RCTs in children/adolescents showed that no antidepressant was superior to placebo apart from fluoxetine, several antidepressants had higher discontinuation rates than placebo, and that venlafaxine increased the risk of suicidality even in the short-term duration of an RCT.[13] Merging lack of efficacy with lack of safety may raise serious concerns on the use of antidepressants in children/adolescents, with an unfavorable benefit/risk ratio. However, lack of superiority of antidepressants over placebo,[12] especially in children, was due to a very high placebo response,

which has been an increasing problem in RCTs in psychiatry. Also, it is possible that increased suicidality in children/adolescents taking antidepressants may be due to ineffectiveness on depressive symptoms in suicidal individuals, rather than to a direct effect of antidepressants. Additionally, our results show that confounding by indication probably drives safety concerns on the use of antidepressants in children/adolescents. Besides, the risk-benefit evaluation in children and adolescents is quite different for antidepressants (predominantly SSRIs) when used for other disorders like anxiety disorders and OCD.[3-5,12]

Conversely, we found highly suggestive evidence supporting a protective role of antidepressants in adults against suicidality,[80] which is consistent with results of a network meta-analysis of RCTs in adults showing that all antidepressants were superior to placebo in reducing depressive symptoms.[10] Similarly, meta-analyses support the efficacy of antidepressants for anxiety disorders [5] and OCD [3] in adults. In adults the benefit/risk ratio must account for clear efficacy of antidepressants and protection against suicide, which should be balanced with other safety concerns rising from the present umbrella review. Overall, several adverse outcomes associated with antidepressants supported by highly suggestive evidence can medically be prevented (i.e., poor bone status, gastro-intestinal bleeding) as previously reported.[82] Hence, benefits of antidepressants in adults and older adults may well trump (preventable) safety issues, given their clear efficacy in treating various psychiatric disorders.[3-5,12] Moreover, the association between antidepressants and certain adverse health outcomes varies within specific age groups. For instance, the increased risk of fractures applies predominantly to an older population that is already prone to poor bone status and multimorbidity,[83] and not in people aged 20-40 years old.

Convincing evidence before accounting for confounding by indication supporting the association between antidepressants and autism, and other offspring adverse health outcomes may call for restriction of antidepressants during pregnancy to those women with high risk of relapse and with severe clinical presentations. Actually, warnings to avoid prescribing medications in early

pregnancy have been already set.[84] However, autism remains a rare event, with a prevalence from cohort studies of <1% according to data pooled in this study. Importantly, the convincing level of evidence was not confirmed when considering confounding by indication, suggesting that the association between antidepressants and autism, suicidality in youth, etc. may be due to effects of the underlying disease, rather than to antidepressants,[39,43,44,50] as recently shown in an umbrella review on risk factors for autism.[85] Comparing two depression-matched groups with and without antidepressant use may be methodologically more solid than adjusting analyses statistically. In addition, several adverse outcomes had small effect sizes on top of low prevalence and of no proof of a causal relationship between antidepressants and adverse health outcomes.

Hence, given that a depressive episode itself can impair adolescents and both maternal and fetal health, individualized and shared clinical decisions about the benefit-risk ratio of antidepressants during adolescence and pregnancy should be implemented, but adolescence and pregnancy should not be considered absolute contraindications to the use of antidepressants.

Limitations

Several limitations should be mentioned. First, we did not grade the evidence from meta-analyses of RCTs, covering a portion of available studies. However, evidence from RCTs is limited by the selection of healthier patients and frequent short-term follow-up, among other factors.[16] Many severe adverse outcomes cannot be addressed in RCTs, and for low frequency and long-term health risks, observational research is the most feasible method.[17] Nevertheless, observational research is not free from bias, either.[18,86] Results from observational studies yield associations, which do not imply causality. Further, results in main analyses are affected by various confounders due to lack of randomization, potential channeling bias, and cofounding by indication.[17,18,80] Specifically, the nature of the control groups was only insufficiently characterized, and there is evidence that when matching (and not adjusting) for the underlying psychiatric disorder, risk differences become smaller or non-significant.[43,44,51] Thus, the association with suicidality may be driven by antidepressants' limited

efficacy in those suicidal children and adolescents according to results from RCTs,[19] rather than being a direct effect of antidepressants on increasing suicidality. Notably, the association between ASD and SSRIs during pregnancy [52] included studies that were not adjusted for confounders (in contrast with weak evidence of any association between any antidepressants during pregnancy and ASD when adjusting for confounders [50] – eTable 4). Moreover, no inference can be made about newer antidepressants (e.g., vortioxetine), which have not been assessed in any of the included meta-analyses. Furthermore, there was insufficient data on cardiometabolic outcomes; an emerging concern of the increased prescribing rates of antidepressants, and crucial area for future research.[87] Finally, our grading system can only provide warnings of the potential presence of systematic biases but cannot provide evidence of their nature and extent[16,32,33] alongside umbrella reviews cannot supply any comparative ranking, as in network meta-analyses.

Conclusions

Our findings are important in the context of increased antidepressant use globally.[1,2] An association between antidepressants and few adverse health outcomes with convincing evidence was observed, yet prevalence of those outcomes was on average low (range 0.1%-9.7%), and after accounting for confounding by indication, no association was supported by convincing evidence. Further research in both RCT and real-world samples matched for underlying disease is needed to confirm a possible causal association between antidepressants and adverse outcomes, considering dose-effect response, mechanistic processes, accounting for patient-specific characteristics, such as age, clinical diagnoses, and severity of clinical condition. No absolute contraindication against the use of antidepressants is currently supported by convincing evidence.

Author Contributions

ED, MS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ED and MS and EE designed the project.

ED and MS searched the literature, extracted the data, ran the analysis, and contributed equally to this work.

All authors (ED, MS AF, PF-P, PD, TT, BS, JF, MF, DT, AFC, EV, PMcG, AHY, JIS, CUC, EE) approved the protocol, and drafted the manuscript, provided critical comments to the paper for important intellectual content, and approved the final version.

Conflict of Interest Disclosures

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Dr. Young is employed by King’s College London; Honorary Consultant SLaM (NHS UK). He gave paid lectures and advisory boards for the following companies with drugs used in affective and

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Data sharing

The data are available from the corresponding author upon reasonable request.

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Tables

Table 1 Criteria for evaluation of the credibility of the evidence of observational studies

Classification	**Criteria**
Convincing evidence (Class I)	1. More than 1000 cases 2. Significant summary associations ($p<1x10^{-6}$) per random-effects calculations 3. No evidence of small-study effects 4. No evidence of excess of significance bias 5. Prediction intervals not including the null value 6. Largest study nominally significant ($p<0.05$) 7. No large heterogeneity (i.e., $I^2< 50\%$)
Highly Suggestive evidence (Class II)	1. More than 1000 cases 2. Significant summary associations ($p<1x10^{-6}$) per random-effects calculation 3. Largest study nominally significant ($p<0.05$)
Suggestive Evidence (Class III)	1. More than 1000 cases 2. Significant summary associations ($p<1x10^{-3}$) per random-effects calculations
Weak evidence (Class IV)	1. All other associations with $p\leq0.05$
Non-significant associations (NS)	1. All associations with $p >0.05$

Table 2 Convincing evidence (Class I) and highly suggestive evidence (Class II) for the association of antidepressants and risk of adverse health outcomes in meta-analyses of observational studies

						Criteria used for classification of level of evidence							
Adverse health outcomes (author, year)	**Exposed/ Unexposed**	**Prevalence (%) based on cohort studies**	**n**	**Random-effects measure, ES (95% CI)**	**Results**	**N cases/ total population**	**p- value random effects**	**I^2 (p-value)**	**PI (95 % CI)**	**SSE/ESB**	**LS**	**CE**	**AMSTAR 2 quality**
Autism spectrum disorders (Pre-pregnancy maternal exposure; Morales, 2018)[51]	Any AD users/ No AD users	0. 8%	7	RR, 1.48 (1.29, 1.71)	Increased risk for ADs	22 877/ 2 400 720	$6.8x10^{-8}$	24 (0.244)	1.09–2.02	No/NP	Yes	I	Moderate
Autism spectrum disorders (pregnancy maternal exposure unadjusted estimates only; Andalib, 2017)[52]	SSRIs / Non-SSRIs users	0. 9%	7	OR, 1.84 (1.60, 2.11)	Increased risk for SSRIs	58 178 / 5 868 692	$1.2x10^{-17}$	0 (0.729)	1.53–2.20	No/NP	Yes	I	Moderate

						Criteria used for classification of level of evidence							
Adverse health outcomes (author, year)	**Exposed/ Unexposed**	**Prevalence (%) based on cohort studies**	**n**	**Random-effects measure, ES (95% CI)**	**Results**	**N cases/ total population**	**p- value random effects**	**I^2 (p-value)**	**PI (95 % CI)**	**SSE/ESB**	**LS**	**CE**	**AMSTAR 2 quality**
Suicide attempt and completion in children and adolescents (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	9. 4%	5	OR, 1.92 (1.51, 2.44)	Increased risk for SSRIs	6 531/ 61 522	$1{\cdot}0x10^{-7}$	0 (0.469)	1.30–2.84	No/NP	Yes	I	High
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6. 5%	24	RR, 1.67 (1.56, 1.80)	Increased risk for SSRIs	136 449/ 1 546 913	$1.3x10^{-44}$	88 (<0.000)	1.23-2.27	No/NP	Yes	II	Moderate
Attention-deficit hyperactivity disorder in children (Man, 2018)[48]	Prenatal exposure to ADs/ No AD users	2. 4%	7	RR, 1.39 (1.21,1.61)	Increased risk for ADs	57 552/ 2 886 904	$5.1x10^{-6}$	79 (<0.000)	0.90–2.15	No/NP	Yes	II	Moderate
Cataract development (Fu, 2018)[49]	TCAs/ non-users or no users of any other AD	NA	3	OR, 1.19 (1.11, 1.28)	Increased risk for TCAs	215 298/ 431 171	$2.0x10^{-6}$	58 (0.092)	0.56-2.52	No/NP	Yes	II	Moderate
Severe bleeding at any site	SSRIs+ SNRIs/ non-users or no	2. 4%	44	OR, 1.41 (1.27,1.57)	Increased risk for	75 215/ 1 443 029	$2.2x10^{-10}$	90 (<0.000)	0.77-2.59	No/No	Yes	II	Low

						Criteria used for classification of level of evidence							
Adverse health outcomes (author, year)	**Exposed/ Unexposed**	**Prevalence (%) based on cohort studies**	**n**	**Random-effects measure, ES (95% CI)**	**Results**	**N cases/ total population**	**p- value random effects**	**I^2 (p-value)**	**PI (95 % CI)**	**SSE/ESB**	**LS**	**CE**	**AMSTAR 2 quality**
(Laporte, 2017)[55]	users of any other AD				SSRIs+ SNRIs								
Postpartum hemorrhage (Jiang, 2016) [58]	Any AD users/ No AD users	6. 8%	17	RR, 1.32 (1.17, 1.48)	Increased risk for ADs	49 155/ 65 1715	$3.3x10^{-6}$	85 (<0.000)	0.84-2.07	No/NP	Yes	II	Low
Upper GI bleeding (Jiang, 2015) [64]	SSRIs+others non-ADs/ No SSRIs use only+others non-ADs	0.7%	22	OR, 1.55 (1.35, 1.78)	Increased risk for SSRIs	56 182/ 592 508	$9.2x10^{-12}$	89 (<0.000)	0.83-2.91	No/No	Yes	II	Moderate
Preterm birth (Huang, 2014) [66]	Any AD users/ No AD users	0. 8%	28	RR, 1.68 (1.52, 1.86)	Increased risk for ADs	24 669/ 3 063709	$3.6x10^{-23}$	44 (0.008)	1.23-2.30	Yes/NP	Yes	II	Moderate
Osteoporotic fractures (Wu, 2013) [70]	TCAs users/ Non-TCAs users	1. 4%	12	RR, 1.45 (1.31, 1.60)	Increased risk for TCAs	178 237/ 831 912	$6.2x10^{-13}$	76 (<0.000)	1.04-2.01	Yes/No	Yes	II	Moderate
Apgar score at 5 minutes	Any AD users/ No AD users	2. 1%	15	SMD, -0.33	Increased risk for ADs	1 473/ 71 828	$7.5x10^{-7}$	58 (0.003)	-1.02, 0.36	No/No	Yes	II	Moderate

						Criteria used for classification of level of evidence							
Adverse health outcomes (author, year)	**Exposed/ Unexposed**	**Prevalence (%) based on cohort studies**	**n**	**Random-effects measure, ES (95% CI)**	**Results**	**N cases/ total population**	**p- value random effects**	**I^2 (p-value)**	**PI (95 % CI)**	**SSE/ESB**	**LS**	**CE**	**AMSTAR 2 quality**
(Ross, 2013) [71]				(-0.47,-0.20)									
Hip Fracture (Oderda, 2012)[76]	TCAs and/or SSRIs users/ No AD users	7. 4%	18	OR, 1.78 (1.53, 2.07)	Increased risk for TCAs or SSRIs	49 276/ 210 577	$5.2x10^{-14}$	89 (<0.000)	1.00-3.19	Yes/Yes	Yes	II	Critically low
Suicide attempt and completion in adults (Barbui, 2009)[80]	SSRIs / Non- SSRIs users	4.5%	7	OR, 0.59 (0.48, 0.72)	Decreased risk for SSRIs	7 164/ 147 383	$5{\cdot}2x10^{-7}$	59 (0.023)	0.33-1.05	No/NP	Yes	II	High

AD–antidepressants, APGAR – acronym of Appearance (skin color), Pulse (heart rate), Grimace (reflex irritability), Activity (muscle tone), and Respiration, CE – class of evidence, CI – confidence interval, ES – effect size, ESB –excess significance bias, GI–gastrointestinal, I^2 –heterogeneity, LS – largest study with significant effect, n – number of included studies per association, N – number of cases, NA– not applicable, NP – not pertinent because the number of observed studies is less than the expected, OR – odds ratio, PI – prediction interval, RR – relative risk, SNRIs – serotonin–norepinephrine reuptake inhibitors, SSRIs – selective serotonin reuptake inhibitors, SMD–standardised mean difference, SSE – small-study effect, TCAs – tricyclic antidepressants.

Table 3 Sensitivity analysis for the associations between antidepressants use and risk of adverse health outcomes of class I-II associations limited to only cohort studies, prospective cohort, studies with adjustments for multiple covariates, studies adjusted for confounding by indication, high-quality studies, classes of antidepressants (SSRIs studies, TCAs studies, other or mixed antidepressants studies), and study location (Europe, North America, other regions)

					Criteria used for classification of level of evidence							
Adverse health outcomes (author, year)	**Exposed/Unexposed**	**Prevalence (%) based on cohort studies**	**n**	**Random-effects measure, ES (95% CI)**	**N cases/ total population**	**p-random effects**	**I^2 (p)**	**PI (95% CI)**	**SSE/ESB**	**LS**	**CE**	**CES / AMSTAR 2**
Cohort studies (both retrospective and prospective)												
Autism spectrum disorders (pregnancy maternal exposure; unadjusted estimates only; Andalib, 2017)[52]	SSRIs/Non-SSRIs users	0. 9%	3	OR, 1.65 (1.37, 2.00)	50 494 / 5 790 186	$2.2x10^{-7}$	0 (0.692)	0.48-5.68	No/No	Yes	I	II/ Moderate
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6. 5%	16	RR, 1.63 (1.49, 1.79)	56 397/ 859 611	$8.9x10^{-27}$	85 (<0.000)	1.20-2.22	No/NP	Yes	II	II/ Moderate

Preterm birth (Huang, 2014)[66]	Any AD users/ Non-AD users	0. 8%	24	RR, 1.67 (1.51, 1.86)	24 378/ 3 063 012	$6.5x10^{-22}$	49 (0.004)	1.21-2.33	Yes/No	Yes	II	II / Moderate
Apgar score at 5 minutes (Ross, 2013)[71]	Any AD users/ Non-AD users	2. 1%	15	SMD, -0.33 (-0.47,-0.20)	1 473/ 71 828	$7.5x10^{-7}$	58 (0.003)	-1.02, 0.36	No/No	Yes	II	II / Moderate
Suicide attempt and completion in children and adolescents (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	9. 4%	3	OR, 1.89 (1.46, 2.43)	5 647/ 59 971	$1.8x10^{-7}$	0 (0.463)	0.36-9.85	No/NP	Yes	I	II / High
Suicide attempt and completion in adults (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	4.5%	5	OR, 0.53 (0.43, 0.66)	6 458/ 143 340	$5.2x10^{-7}$	55 (0.064)	0.27-1.04	No/NP	Yes	II	II / High
Prospective cohort studies												
Autism spectrum disorders (pregnancy maternal exposure; unadjusted estimates only; Andalib, 2017)[52]	SSRIs/Non-SSRIs users	0. 9%	3	OR, 1.65 (1.37, 2.00)	50 494 / 5 790 186	$2.2x10^{-7}$	0 (0.692)	0.48-5.68	No/No	Yes	I	II/ Moderate
Preterm birth (Huang, 2014)[66]	Any AD users/ Non-AD users	0. 4%	11	RR, 1.87 (1.52, 2.30)	2 540/ 690 121	$3.4x10^{-9}$	31 (0.148)	1.17-3.00	No/NP	Yes	II	I / Moderate
Studies with adjustments for multiple covariates												
Autism spectrum disorders (Pre-pregnancy maternal exposure; Morales, 2018)[51]	Any AD users/ No AD users	0. 8%	7	RR, 1.48 (1.29, 1.71)	22 877/ 2 400 720	$6.8x10^{-8}$	24 (0.244)	1.09–2.02	No/NP	Yes	I	I/ Moderate

Suicide attempt and completion in children and adolescents (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	9. 4%	5	OR, 1.92 (1.51, 2.44)	6 531/ 61 522	$1.0x10^{-7}$	0 (0.469)	1.30–2.84	No/NP	Yes	I	I / High
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6.5%	22	RR, 1.67 (1.53, 1.82)	96 353/ 929 936	$6.6x10^{-33}$	88 (<0.000)	1.17-2.38	No/NP	Yes	II	II/ Moderate
Attention-deficit hyperactivity disorder in children (Man, 2018)[48]	Prenatal exposure to ADs/ No AD users	2. 4%	7	RR, 1.39 (1.21,1.61)	57 552/ 2 886 904	$5.1x10^{-6}$	79 (<0.000)	0.90–2.15	No/NP	Yes	II	II/ Moderate
Upper GI bleeding (Jiang, 2015) [64]	SSRIs+others non-ADs/ No SSRIs use only+others non-ADs	1.3%	15	RR, 1.48 (1.32, 1.67)	43 571/ 308 060	$1.3x10^{-10}$	61 (0.001)	1.00-2.20	No/NP	Yes	II	II / Moderate
Osteoporotic fractures (Wu, 2013)[70]	TCAs users/ Non-TCAs users	NA	11	RR, 1.43 (1.29, 1.58)	178 237 / 740 768	$1.9 x10^{-12}$	77 (<0.000)	1.04-1.97	Yes/No	Yes	II	II / Moderate
Hip Fracture (Oderda, 2012)	TCAs and/or SSRIs users/ No AD users	NA	14	OR, 1.76 (1.49, 2.08)	47 762/ 198 820	$1.9x10^{-11}$	92 (0.001)	0.96-3.24	Yes/No	Yes	II	II / Critically low
Studies adjusted for confounding by indication												
Autism spectrum disorders (Pre-pregnancy maternal exposure; Morales, 2018)[51]	Any AD users/ No AD users	1.1%	3	RR, 1.69 (1.39, 2.05)	3 016/ 667 431	$1.0 x10^{-7}$	0 (0.735)	0.48–5.94	No/No	Yes	I	II/ Moderate

Suicide attempt and completion in children and adolescents (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	9.7%	4	OR, 2.04 (1.23, 3,41)	5 522 / 55 124	0.006	16 (0.314)	0.47-8.81	Yes/NP	No	I	IV / High
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6.3%	11	RR, 1.61 (1.43, 1.82)	54 023/ 645 463	$1.0x10^{-14}$	88 (<0.000)	1.08-2.41	No/NP	Yes	II	II/ Moderate
Osteoporotic fractures (Wu, 2013)[70]	TCAs users/ Non-TCAs users	NA	7	RR, 1.47 (1.23, 1.69)	156 374/ 659 389	$5.0x10^{-8}$	62 (0.021)	0.98-2.22	No/No	Yes	II	II / Moderate
High-quality primary studies												
Autism spectrum disorders (Pre-pregnancy maternal exposure; Morales, 2018)[51]	Any AD users/ No AD users	0. 8%	7	RR, 1.48 (1.29, 1.71)	22 877/ 2 400 720	$6.8x10^{-8}$	24 (0.244)	1.09–2.02	No/NP	Yes	I	I/ Moderate
Autism spectrum disorders (pregnancy maternal exposure; unadjusted estimates only; Andalib, 2017)[52]	SSRIs / Non-SSRIs users	0. 9%	7	OR, 1.84 (1.60, 2.11)	58 178 / 5 868 692	$1.2x10^{-17}$	0 (0.729)	1.53–2.20	No/NP	Yes	I	I/ Moderate
Suicide attempt and completion in children and adolescents (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	3.6%	4	OR, 1.88 (1.47, 2.40)	5 961/ 30 343	$3.5x10^{-7}$	0 (0.496)	1.10-3.21	No/NP	Yes	I	I/ High
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6. 6%	20	RR, 1.70 (1.57, 1.85)	117 567/ 1 053 697	$9.6x10^{-37}$	88 (<0.000)	1.23-2.35	No/NP	Yes	II	II/ Moderate
Attention-deficit hyperactivity disorder in children	Prenatal exposure to ADs/ No AD users	2. 4%	7	RR, 1.39 (1.21,1.61)	57 552/ 2 886 904	$5.1x10^{-6}$	79 (<0.000)	0.90–2.15	No/NP	Yes	II	II/ Moderate

(Man, 2018)[48]												
Postpartum hemorrhage (Jiang, 2016)[58]	Any AD users/ No AD users	6. 8%	16	RR, 1.32 (1.17, 1.48)	49 142/ 651 439	$3.7x10^{-6}$	86 (<0.000)	0.84-2.08	No/NP	Yes	II	II Low
Preterm birth (Huang, 2014)[66]	Any AD users/ No AD users	0. 3%	19	RR, 1.86 (1.59, 2.19)	5 116/ 1 658 666	$5.3x10^{-14}$	52 (0.004)	1.16-3.00	Yes/No	Yes	II	II/ Moderate
Osteoporotic fractures (Wu, 2013)[70]	TCAs users/ Non-TCAs users	NA	9	RR, 1.46 (1.30, 1.65)	36 865/ 247 078	$6.0x10^{-10}$	82 (<0.000)	0.99-2.15	Yes /NP	Yes	II	II/ Moderate
Hip Fracture (Oderda, 2012)[76]	TCAs and/or SSRIs users/ No AD users	NA	6	OR, 1.59 (1.31, 1.92)	41 227/ 159 831	$2.5x10^{-7}$	91 (<0.000)	0.82-3.07	Yes/No	Yes	II	II/ Critically low
Suicide attempt and completion in adults (Barbui, 2009)[80]	SSRIs / Non- SSRIs users	4.5%	7	OR, 0.59 (0.48, 0.72)	7 164/ 147 383	$5.2x10^{-7}$	59 (0.023)	0.33-1.05	No/NP	Yes	II	II/ High
SSRIs studies												
Autism spectrum disorders (pregnancy maternal exposure; unadjusted estimates only; Andalib, 2017) [52]	SSRIs / Non-SSRIs users	0. 9%	7	OR, 1.84 (1.60, 2.11)	58 178 / 5 868 692	$1.2x10^{-17}$	0 (0.729)	1.53–2.20	No/NP	Yes	I	I/ Moderate
Suicide attempt and completion in children and adolescents (Barbui, 2009)[80]	SSRIs / Non-SSRIs users	9. 4%	5	OR, 1.92 (1.51, 2.44)	6 531/ 61 522	$1.0x10^{-7}$	0 (0.469)	1.30–2.84	No/NP	Yes	I	I / High
Apgar score at 5 minutes (Ross, 2013)[71]	SSRIs / Non-SSRIs users	5. 7%	13	SMD, -0.27 (-0.37, -0.16)	1 127/ 19 695	$2.1x10^{-7}$	35 (0.100)	-0.53, -0.01	No/No	Yes	II	I / Moderate

Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6. 5%	24	RR, 1.67 (1.56, 1.80)	136 449/ 1 546 913	$1.3x10^{-44}$	88 (<0.000)	1.23-2.27	No/NP	Yes	II	II/ Moderate
Preterm birth (Huang, 2014)[66]	SSRIs / Non-SSRIs users	9. 7%	20	RR, 1.73 (1.53, 1.96)	21 163/ 2 153 680	$3.6x10^{-23}$	48 (0.009)	1.22-2.46	Yes/NP	Yes	II	II / Moderate
Suicide attempt and completion in adults (Barbui, 2009)[80]	SSRIs / Non- SSRIs users	3. 5%	7	OR, 0.59 (0.48, 0.72)	7 164/ 147 383	$5.2x10^{-7}$	59 (0.023)	0.33-1.05	No/NP	Yes	II	II / High
TCAs studies												
Cataract development (Fu, 2018)[49]	TCAs/ non-users or no users of any other AD	NA	3	OR, 1.19 (1.11, 1.28)	215 298/ 431 171	$2.0x10^{-6}$	58 (0.092)	0.56-2.52	No/NP	Yes	II	II / Moderate
Osteoporotic fractures (Wu, 2013)[70]	TCA users/ Non-TCA users	1. 4%	12	RR, 1.45 (1.31, 1.60)	178 237/ 831 912	$6.2x10^{-13}$	76 (<0.000)	1.04-2.01	Yes/No	Yes	II	II / Moderate
Other or mixed AD studies												
Autism spectrum disorders (Pre-pregnancy maternal exposure; Morales, 2018)[51]	Other or mixed/Non-users	0. 8%	7	RR, 1.48 (1.29, 1.71)	22 877/ 2 400 720	$6.8x10^{-8}$	24 (0.244)	1.09–2.02	No/NP	Yes	I	I / Moderate
Preterm birth (Huang, 2014)[66]	Other or mixed/Non-users	0. 4%	8	RR, 1.59 (1.31, 1.93)	3 506/ 910 029	$3.4x10^{-7}$	35 (0.148)	1.02-2.47	No/NP	Yes	II	I / Moderate

Severe bleeding at any site (Laporte, 2017)[55]	Other or mixed/Non-users	6. 8%	44	OR, 1.41 (1.27,1.57)	190 016/ 1 512 411	$2.2x10^{-10}$	90 (<0.000)	0.77-2.59	No/No	Yes	II	II / Low
Postpartum hemorrhage (Jiang, 2016)[58]	Other or mixed/Non-users	6. 8%	17	RR, 1.32 (1.17, 1.48)	49 155/ 65 1715	$3.3x10^{-6}$	85 (<0.000)	0.84-2.07	No/NP	Yes	II	II / Low
Upper GI bleeding (Jiang, 2015) [64]	Other or mixed	0. 7%	22	OR, 1.55 (1.35, 1.78)	56 182/ 592 508	$9.2x10^{-12}$	89 (<0.000)	0.83-2.91	No/No	Yes	II	II / Moderate
European studies												
Autism spectrum disorders (pregnancy maternal exposure; unadjusted estimates only; Andalib, 2017)[52]	SSRIs / Non-SSRIs users	0. 1%	4	OR, 1.80 (1.54, 2.10)	6 394/ 5 741 029	$1.1x10^{-13}$	0 (0.396)	1.28–2.53	No/No	Yes	I	I/ Moderate
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	6. 5%	12	RR, 1.76 (1.68, 1.87)	92 760/ 1 228 807	$2.3x10^{-86}$	67 (<0.000)	1.50-2.07	No/No	Yes	II	II/ Moderate
Upper GI bleeding (Jiang, 2015) [64]	SSRIs+others non-ADs/ No SSRIs use only+others non-ADs	0. 4%	14	OR, 1.60 (1.33, 1.93)	46 594/ 236 085	$4.8x10^{-7}$	86 (<0.000)	0.80-3.91	No/NP	Yes	II	II / Moderate
Preterm birth (Huang, 2014)[66]	Any AD users/ No AD users	0. 9%	7	RR, 1.61 (1.36, 1.92)	17 518/ 1 984 543	$5.6x10^{-8}$	56 (0.033)	1.02-2.55	No/NP	Yes	II	II / Moderate
Osteoporotic fractures (Wu, 2013)[70]	TCAs users/ Non-TCAs users	NA	6	RR, 1.37 (1.19, 1.56)	164 476/ 724 914	$6.6x10^{-6}$	69 (0.007)	0.91-2.05	No/NP	Yes	II	II / Moderate

Hip Fracture (Oderda, 2012)[76]	TCAs and/or SSRIs users/ No AD users	2.1%	8	OR, 1.74 (1.39, 2.17)	40 196/ 159 706	$1.1x10^{-6}$	89 (<0.000)	0.88.3.42	Yes/No	Yes	II	II / Critically low
North America studies												
Osteoporotic fractures (Khanassov, 2018)[42]	SSRIs / Non-SSRIs users	5.2 %	10	RR, 1.56 (1.33, 1.84)	31 683/ 249 808	$1.0x10^{-7}$	87 (<0.000)	0.91-2.70	No/NP	Yes	II	II/ Moderate
Preterm birth (Huang, 2014)[66]	Any AD users/ No AD users	0.6%	17	RR, 1.70 (1.44, 1.99)	6 129/ 928 528	$1.2x10^{-10}$	29 (0.124)	1.17-2.45	Yes/NP	Yes	II	II/ Moderate
Osteoporotic fractures (Wu, 2013)[70]	TCAs users/ Non-TCAs users	NA	6	RR, 1.54 (1.32, 1.81)	13 761 / 84 583	$7.3 x10^{-8}$	76 (0.001)	0.95-2.51	No/No	Yes	II	II/ Moderate
Hip Fracture (Oderda, 2012)[76]	TCAs and/or SSRIs users/ No AD users	2.5%	8	OR, 1.81 (1.51, 2.18)	8 654/ 49 024	$2.8x10^{-10}$	82 (<0.000)	1.01-3.27	No/NP	Yes	II	II/ Critically low
Other regions												
None	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA/ NA

AD–antidepressants, CE- class of evidence (main analysis), CES – class of evidence after sensitivity analysis, CI – confidence interval, ES – effect size, ESB –excess significance bias, GI–gastrointestinal, I^2 –heterogeneity, LS – largest study with significant effect, n – number of included studies per association, N – number of cases, NA– not applicable, NP – not pertinent because the number of observed studies is less than the expected, OR – odds ratio, PI – prediction interval, RR – relative risk, SNRIs – serotonin–norepinephrine reuptake inhibitors, SSRIs – selective serotonin reuptake inhibitors, SMD–standardized mean difference, SSE – small-study effect, TCAs – tricyclic antidepressants.

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(("serotonin uptake inhibitors"[Pharmacological Action] OR "serotonin uptake inhibitors"[MeSH Terms] OR ("serotonin"[All Fields] AND "uptake"[All Fields] AND "inhibitors"[All Fields]) OR "serotonin uptake inhibitors"[All Fields] OR ("selective"[All Fields] AND "serotonin"[All Fields] AND "reuptake"[All Fields] AND "inhibitors"[All Fields]) OR "selective serotonin reuptake inhibitors"[All Fields]) OR ("serotonin uptake inhibitors"[Pharmacological Action] OR "serotonin uptake inhibitors"[MeSH Terms] OR ("serotonin"[All Fields] AND "uptake"[All Fields] AND "inhibitors"[All Fields]) OR "serotonin uptake inhibitors"[All Fields] OR "ssris"[All Fields]) OR ("antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields]) OR "antidepressive agents"[All Fields] OR "antidepressants"[All Fields]) OR (antidepranalgesia[All Fields] OR antidepredatory[All Fields] OR antideprein[All Fields] OR antidepres[All Fields] OR antidepres'iva[All Fields] OR antidepres'ivn'i[All Fields] OR antidepres'ivn'ich[All Fields] OR antidepres'ivy[All Fields] OR antidepresan[All Fields] OR antidepresant[All Fields] OR antidepresanti[All Fields] OR antidepresants[All Fields] OR antidepresantu[All Fields] OR antidepresessant[All Fields] OR antidepreseurs[All Fields] OR antidepresiv[All Fields] OR antidepresiva[All Fields] OR antidepresivach[All Fields] OR antidepresivami[All Fields] OR antidepresivas[All Fields] OR antidepresive[All Fields] OR antidepresivem[All Fields] OR antidepresives[All Fields] OR antidepresivi[All Fields] OR antidepresivima[All Fields] OR antidepresivinm[All Fields] OR antidepresivnaih[All Fields] OR antidepresivni[All Fields] OR antidepresivnich[All Fields] OR antidepresivniho[All Fields] OR antidepresivnim[All Fields] OR antidepresivnimu[All Fields] OR antidepresivnych[All Fields] OR antidepresivo[All Fields] OR antidepresivos[All Fields] OR antidepresivum[All Fields] OR antidepresivy[All Fields] OR antidepresor[All Fields] OR antidepress[All Fields] OR antidepressand[All Fields] OR antidepressani[All Fields] OR antidepressanov[All Fields] OR antidepressans[All Fields] OR antidepressant[All Fields] OR antidepressant'[All Fields] OR antidepressant's[All Fields] OR antidepressanta[All Fields] OR antidepressantam[All Fields] OR antidepressantami[All Fields] OR antidepressanteffects[All Fields] OR antidepressantinduced[All Fields] OR antidepressantlike[All Fields] OR antidepressantlithium[All Fields] OR antidepressantnogo[All Fields] OR antidepressantom[All Fields] OR antidepressantov[All Fields] OR antidepressants[All Fields] OR antidepressants'[All Fields] OR antidepressantswere[All Fields] OR antidepressantu[All Fields] OR antidepressantv[All Fields] OR antidepressanty[All Fields] OR antidepressed[All Fields] OR antidepressent[All Fields] OR antidepressents[All Fields] OR antidepresseur[All Fields] OR antidepresseurs[All Fields] OR antidepresseurs'[All Fields] OR antidepresseus[All Fields] OR antidepresseuses[All Fields] OR antidepressia[All Fields] OR antidepressief[All Fields] OR antidepressieve[All Fields] OR antidepressiewe[All Fields] OR antidepressif[All Fields] OR antidepressifs[All Fields] OR antidepressiivien[All Fields] OR antidepressiiviset[All Fields] OR antidepressin[All Fields] OR antidepressing[All Fields] OR antidepression[All Fields] OR antidepressions[All Fields] OR antidepressionsbehandling[All Fields] OR antidepressiu[All Fields] OR antidepressiv[All Fields] OR antidepressiva[All Fields] OR antidepressivabehandling[All Fields] OR antidepressivarichtlijnen[All Fields] OR antidepressivas[All Fields] OR antidepressivastudien[All Fields] OR antidepressivasubstanzen[All Fields] OR antidepressivatherapie[All Fields] OR antidepressive[All Fields] OR antidepressively[All Fields] OR antidepressivem[All Fields] OR antidepressiven[All Fields] OR antidepressivene[All Fields] OR antidepressiver[All Fields] OR antidepressives[All Fields] OR antidepressivi[All Fields] OR antidepressivnikh[All Fields] OR antidepressivnoe[All Fields] OR antidepressivnogo[All Fields] OR antidepressivnoi[All Fields] OR antidepressivnom[All Fields] OR antidepressivnye[All Fields] OR antidepressivnyi[All Fields] OR antidepressivnykh[All Fields] OR antidepressivnymi[All Fields] OR antidepressivo[All Fields] OR antidepressivos[All Fields] OR antidepressivt[All Fields] OR antidepressivum[All Fields] OR antidepressivum'[All Fields] OR antidepressivums[All Fields] OR

antidepressziv[All Fields] OR antidepresszivum[All Fields] OR antidepresszivumhasznalat[All Fields] OR antidepresszivumok[All Fields] OR antidepresszivumot[All Fields] OR antideprimenti[All Fields] OR antideprin[All Fields] OR antideprssants[All Fields] OR antideprssiva[All Fields] OR antideprssives[All Fields]) OR ("citalopram"[MeSH Terms] OR "citalopram"[All Fields]) OR ("citalopram"[MeSH Terms] OR "citalopram"[All Fields] OR "escitalopram"[All Fields]) OR ("fluoxetine"[MeSH Terms] OR "fluoxetine"[All Fields]) OR ("fluvoxamine"[MeSH Terms] OR "fluvoxamine"[All Fields]) OR ("paroxetine"[MeSH Terms] OR "paroxetine"[All Fields]) OR ("sertraline"[MeSH Terms] OR "sertraline"[All Fields]) OR ("monoamine oxidase inhibitors"[Pharmacological Action] OR "monoamine oxidase inhibitors"[MeSH Terms] OR ("monoamine"[All Fields] AND "oxidase"[All Fields] AND "inhibitors"[All Fields]) OR "monoamine oxidase inhibitors"[All Fields] OR "maoi"[All Fields]) OR ("antidepressive agents, tricyclic"[Pharmacological Action] OR "antidepressive agents, tricyclic"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields] AND "tricyclic"[All Fields]) OR "tricyclic antidepressive agents"[All Fields] OR ("tricyclic"[All Fields] AND "antidepressant"[All Fields]) OR "tricyclic antidepressant"[All Fields]) OR ("Theor Chem Acc"[Journal] OR "tca"[All Fields]) OR (("serotonin"[MeSH Terms] OR "serotonin"[All Fields]) AND ("norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields] OR "noradrenaline"[All Fields]) AND reuptake[All Fields] AND inhibitor[All Fields]) OR ("serotonin and noradrenaline reuptake inhibitors"[Pharmacological Action] OR "serotonin and noradrenaline reuptake inhibitors"[MeSH Terms] OR ("serotonin"[All Fields] AND "noradrenaline"[All Fields] AND "reuptake"[All Fields] AND "inhibitors"[All Fields]) OR "serotonin and noradrenaline reuptake inhibitors"[All Fields] OR "snri"[All Fields]) OR (("serotonin antagonists"[Pharmacological Action] OR "serotonin antagonists"[MeSH Terms] OR ("serotonin"[All Fields] AND "antagonists"[All Fields]) OR "serotonin antagonists"[All Fields] OR ("serotonin"[All Fields] AND "antagonist"[All Fields]) OR "serotonin antagonist"[All Fields]) AND reuptake[All Fields] AND inhibitor[All Fields]) OR SARI[All Fields] OR (("norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields]) AND ("dopamine uptake inhibitors"[Pharmacological Action] OR "dopamine uptake inhibitors"[MeSH Terms] OR ("dopamine"[All Fields] AND "uptake"[All Fields] AND "inhibitors"[All Fields]) OR "dopamine uptake inhibitors"[All Fields] OR ("dopamine"[All Fields] AND "reuptake"[All Fields] AND "inhibitor"[All Fields]) OR "dopamine reuptake inhibitor"[All Fields])) OR NDRI[All Fields] OR (("norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields]) AND reuptake[All Fields] AND inhibitor[All Fields]) OR NRI[All Fields] OR (noradrenergic[All Fields] AND specific[All Fields] AND serotonergic[All Fields] AND ("antidepressive agents"[Pharmacological Action] OR "antidepressive agents"[MeSH Terms] OR ("antidepressive"[All Fields] AND "agents"[All Fields]) OR "antidepressive agents"[All Fields] OR "antidepressant"[All Fields])) OR NaSSA[All Fields]) AND (("suicide"[MeSH Terms] OR "suicide"[All Fields]) OR ("suicidal ideation"[MeSH Terms] OR ("suicidal"[All Fields] AND "ideation"[All Fields]) OR "suicidal ideation"[All Fields]) OR (("suicide"[MeSH Terms] OR "suicide"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) OR (serious[All Fields] AND adverse[All Fields] AND events[All Fields]) OR ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields] OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields]) OR harm[All Fields] OR ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR ("bone"[All Fields] AND "fractures"[All Fields])) OR ("psychomotor agitation"[MeSH Terms] OR ("psychomotor"[All Fields] AND "agitation"[All Fields]) OR "psychomotor agitation"[All Fields] OR "akathisia"[All Fields]) OR ("photosensitivity disorders"[MeSH Terms] OR ("photosensitivity"[All Fields] AND "disorders"[All Fields]) OR "photosensitivity disorders"[All Fields] OR "photosensitivity"[All Fields]) OR (("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All Fields]) AND ("physiopathology"[Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields])) OR ("coronary disease"[MeSH Terms] OR ("coronary"[All Fields] AND "disease"[All Fields]) OR "coronary disease"[All Fields] OR ("coronary"[All Fields] AND "heart"[All Fields] AND "disease"[All Fields]) OR

"coronary heart disease"[All Fields]) OR ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields]) OR (("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) OR (discontinuation[All Fields] AND ("syndrome"[MeSH Terms] OR "syndrome"[All Fields])) OR ("serotonin syndrome"[MeSH Terms] OR ("serotonin"[All Fields] AND "syndrome"[All Fields]) OR "serotonin syndrome"[All Fields]) OR ("neonatal abstinence syndrome"[MeSH Terms] OR ("neonatal"[All Fields] AND "abstinence"[All Fields] AND "syndrome"[All Fields]) OR "neonatal abstinence syndrome"[All Fields]) OR ("autistic disorder"[MeSH Terms] OR ("autistic"[All Fields] AND "disorder"[All Fields]) OR "autistic disorder"[All Fields] OR "autism"[All Fields])) AND (("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]) OR ("meta-analysis as topic"[MeSH Terms] OR ("meta-analysis"[All Fields] AND "topic"[All Fields]) OR "meta-analysis as topic"[All Fields] OR "metaanalysis"[All Fields]) OR "systematic review"[All Fields])

eTable 1 Articles excluded after full-text revision, with reasons

Author, year (Reference)	Reason for exclusion
Ng, 2019 [1]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Patel, 2019 [2]	Not reporting an association of antidepressants and risk of adverse health outcomes
Rexwinkel, 2019 [3]	Nether a meta-analysis or systematic review with quantitative synthesis
Perlman, 2019 [4]	Nether a meta-analysis or systematic review with quantitative synthesis
Amare, 2019 [5]	Not reporting an association of antidepressants and risk of adverse health outcomes
Aguiar, 2019 [6]	Nether a meta-analysis or systematic review with quantitative synthesis
Zhou, 2018[7]	Not included only case-control and cohort studies
Wu, 2018 [8]	Not reporting an association of antidepressants and risk of adverse health outcomes
Wang, 2018 [9]	Nether a meta-analysis or systematic review with quantitative synthesis
Visco, 2018[10]	Not included only case-control and cohort studies
Uguz, 2018 [11]	Nether a meta-analysis or systematic review with quantitative synthesis
Tan, 2018[12]	Not a meta-analysis or systematic review of observational studies
Telang, 2018 [13]	Not a meta-analysis or systematic review of observational studies
Sepehripour, 2018[14]	Nether a meta-analysis or systematic review with quantitative synthesis
Prady, 2018 [15]	Nether a meta-analysis or systematic review with quantitative synthesis
Cappetta, 2018[16]	Not a meta-analysis or systematic review of observational studies
Steinert, 2018[17]	Nether a meta-analysis or systematic review with quantitative synthesis
Melo, 2018[18]	Not included only case-control and cohort studies
Moncrieff, 2018[19]	Nether a meta-analysis or systematic review with quantitative synthesis
Douros, 2018 [20]	Nether a meta-analysis or systematic review with quantitative synthesis
Chen, 2018[21]	Not a meta-analysis or systematic review of observational studies
Comoretto, 2018 [22]	Not reporting an association of antidepressants and risk of adverse health outcomes
Varney, 2017 [23]	Nether a meta-analysis or systematic review with quantitative synthesis
Uguz, 2017 [24]	Nether a meta-analysis or systematic review with quantitative synthesis
Salvi, 2017[25]	Not included only case-control and cohort studies
Stubbs, 2017 [26]	Nether a meta-analysis or systematic review with quantitative synthesis
Riediger, 2017 [27]	Not a meta-analysis or systematic review of observational studies
Querido, 2017 [28]	Nether a meta-analysis or systematic review with quantitative synthesis
Mezzacappa, 2017[29]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Maund, 2017 [30]	Not a meta-analysis or systematic review of observational studies
Moraros, 2017[31]	Not included only case-control and cohort studies
Locher, 2017 [32]	Not a meta-analysis or systematic review of observational studies
Laux, 2017 [33]	Nether a meta-analysis or systematic review with quantitative synthesis
Kaplan, 2017 [34]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Heller, 2017 [35]	Nether a meta-analysis or systematic review with quantitative synthesis
Hill, 2017[36]	Not included only case-control and cohort studies
Deidda, 2017 [37]	Nether a meta-analysis or systematic review with quantitative synthesis
Brunnauer, 2017 [38]	Nether a meta-analysis or systematic review with quantitative synthesis

Brown, 2017 [39]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Beyer, 2017 [40]	Not a meta-analysis or systematic review of observational studies
Andrade, 2017 [41]	Nether a meta-analysis or systematic review with quantitative synthesis
Allain, 2017 [42]	Nether a meta-analysis or systematic review with quantitative synthesis
Vlachos, 2016 [43]	Nether a meta-analysis or systematic review with quantitative synthesis
Werneke, 2016 [44]	Not reporting an association of antidepressants and risk of adverse health outcomes
Warden, 2016 [45]	Nether a meta-analysis or systematic review with quantitative synthesis
Torjesen, 2016 [46]	Commentary
Stone, 2016 [47]	Commentary
Smit, 2016 [48]	Nether a meta-analysis or systematic review with quantitative synthesis
Simonsen, 2016 [49]	Nether a meta-analysis or systematic review with quantitative synthesis
Sharma, 2016 [50]	Nether a meta-analysis or systematic review with quantitative synthesis
Selmer, 2016 [51]	Insufficient or inadequate data for quantitative synthesis provided
Rudisill, 2016 [52]	Insufficient or inadequate data for quantitative synthesis provided
Pozzi, 2016 [53]	Nether a meta-analysis or systematic review with quantitative synthesis
Potočnjak, 2016 [54]	Nether a meta-analysis or systematic review with quantitative synthesis
Muzik, 2016 [55]	Nether a meta-analysis or systematic review with quantitative synthesis
Lassen, 2016 [56]	Insufficient or inadequate data for quantitative synthesis provided
Kaplan, 2016 [57]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Kobayashi, 2016 [58]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Jordan, 2016 [59]	Nether a meta-analysis or systematic review with quantitative synthesis
Jarde, 2016 [60]	Not reporting an association of antidepressants and risk of adverse health outcomes
Howland, 2016 [61]	Nether a meta-analysis or systematic review with quantitative synthesis
Galling, 2016 [62]	Not reporting an association of antidepressants and risk of adverse health outcomes
Donneyong, 2016 [63]	Nether a meta-analysis or systematic review with quantitative synthesis
Cameron, 2016 [64]	Nether a meta-analysis or systematic review with quantitative synthesis
Braun, 2016 [65]	Not a meta-analysis or systematic review of observational studies
Bielefeldt, 2016 [66]	Not a meta-analysis or systematic review of observational studies
Barth, 2016 [67]	Not a meta-analysis or systematic review of observational studies
Akioyamen, 2016 [68]	Nether a meta-analysis or systematic review with quantitative synthesis
Alvares, 2016[69]	Not included only case-control and cohort studies
Wang, 2015 [70]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Uchida, 2015 [71]	Nether a meta-analysis or systematic review with quantitative synthesis
Thase, 2015 [72]	Nether a meta-analysis or systematic review with quantitative synthesis
Teo, 2015 [73]	Nether a meta-analysis or systematic review with quantitative synthesis
Tampi, 2015 [74]	Nether a meta-analysis or systematic review with quantitative synthesis
Stubbs, 2015 [75]	Commentary
Santarsieri, 2015 [76]	Nether a meta-analysis or systematic review with quantitative synthesis
Robinson, 2015 [77]	Commentary
Renoux, 2015 [78]	Nether a meta-analysis or systematic review with quantitative synthesis
Pinheiro, 2015 [79]	Insufficient or inadequate data for quantitative synthesis provided

Orsolini, 2015 [80]	Nether a meta-analysis or systematic review with quantitative synthesis
Olfson, 2015 [81]	Nether a meta-analysis or systematic review with quantitative synthesis
Nezafati, 2015 [82]	Nether a meta-analysis or systematic review with quantitative synthesis
Mohler, 2015 [83]	Commentary
Man, 2015 [84]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
KoKoAung, 2015 [85]	Full-text could not retrieved
Gøtzsche, 2015 [86]	Commentary
Gentile, 2015 [87]	Nether a meta-analysis or systematic review with quantitative synthesis
Gentile, 2015 [88]	Nether a meta-analysis or systematic review with quantitative synthesis
Gebara, 2015 [89]	Nether a meta-analysis or systematic review with quantitative synthesis
Ennis, 2015 [90]	Not reporting an association of antidepressants and risk of adverse health outcomes
Davis, 2015 [91]	Not reporting an association of antidepressants and risk of adverse health outcomes
Correll, 2015 [92]	Nether a meta-analysis or systematic review with quantitative synthesis
Bruning, 2015 [93]	Nether a meta-analysis or systematic review with quantitative synthesis
Stevenson, 2014 [94]	Nether a meta-analysis or systematic review with quantitative synthesis
Ross, 2014 [95]	Commentary
Rais, 2014 [96]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Park, 2015[97]	Not included only case-control and cohort studies
Prieto-Alhambra, 2014 [98]	Nether a meta-analysis or systematic review with quantitative synthesis
Previti, 2014 [99]	Nether a meta-analysis or systematic review with quantitative synthesis
Pereira, 2014 [100]	Nether a meta-analysis or systematic review with quantitative synthesis
Pedersen, 2014 [101]	Nether a meta-analysis or systematic review with quantitative synthesis
Paumgartten, 2014 [102]	Nether a meta-analysis or systematic review with quantitative synthesis
Okazaki, 2014 [103]	Nether a meta-analysis or systematic review with quantitative synthesis
Oka, 2014 [104]	Insufficient or inadequate data for quantitative synthesis provided
McDonagh, 2014 [105]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Mahdanian, 2014 [106]	Nether a meta-analysis or systematic review with quantitative synthesis
Mago, 2014 [107]	Nether a meta-analysis or systematic review with quantitative synthesis
Lorenzo, 2014 [108]	Nether a meta-analysis or systematic review with quantitative synthesis
Li, 2014 [109]	Nether a meta-analysis or systematic review with quantitative synthesis
Isacsson, 2014 [110]	Nether a meta-analysis or systematic review with quantitative synthesis
Grigoriadis, 2014 [111]	Nether a meta-analysis or systematic review with quantitative synthesis
Gebara, 2014 [112]	Nether a meta-analysis or systematic review with quantitative synthesis
Fanoe, 2014 [113]	Nether a meta-analysis or systematic review with quantitative synthesis
El Marroun, 2014 [114]	Nether a meta-analysis or systematic review with quantitative synthesis
Costoloni, 2014 [115]	Nether a meta-analysis or systematic review with quantitative synthesis
Clayton, 2014 [116]	Nether a meta-analysis or systematic review with quantitative synthesis
Beach, 2014 [117]	Insufficient or inadequate data for quantitative synthesis provided
Anglin, 2014 [118]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Andrade, 2014 [119]	Nether a meta-analysis or systematic review with quantitative synthesis
Rotella, 2013 [120]	Not reporting an association of antidepressants and risk of adverse health outcomes

Rabenda, 2013 [121]	Insufficient or inadequate data for quantitative synthesis provided
Painuly, 2013[122]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Nassir, 2013 [123]	Nether a meta-analysis or systematic review with quantitative synthesis
Myles, 2013 [124]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Mintzes, 2013 [125]	Commentary
Kennedy, 2013 [126]	Commentary
Howland, 2013 [127]	Nether a meta-analysis or systematic review with quantitative synthesis
Grigoriadis, 2013 [128]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Grigoriadis, 2013 [129]	Nether a meta-analysis or systematic review with quantitative synthesis
Gahr, 2013 [130]	Nether a meta-analysis or systematic review with quantitative synthesis
De Jong, 2013 [131]	Nether a meta-analysis or systematic review with quantitative synthesis
De Groot, 2013 [132]	Nether a meta-analysis or systematic review with quantitative synthesis
Brunnauer, 2013 [133]	Nether a meta-analysis or systematic review with quantitative synthesis
Bhattacharjee, 2013 [134]	Not included only case-control and cohort studies
Barnard, 2013 [135]	Nether a meta-analysis or systematic review with quantitative synthesis
Al-Zoairy, 2013 [136]	Nether a meta-analysis or systematic review with quantitative synthesis
Wu, 2012 [137]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
T Jong, 2012 [138]	Nether a meta-analysis or systematic review with quantitative synthesis
Sansone, 2012 [139]	Nether a meta-analysis or systematic review with quantitative synthesis
Pan, 2012 [140]	Nether a meta-analysis or systematic review with quantitative synthesis
Oyebode, 2012 [141]	Nether a meta-analysis or systematic review with quantitative synthesis
Nischal, 2012 [142]	Nether a meta-analysis or systematic review with quantitative synthesis
Malm, 2012 [143]	Nether a meta-analysis or systematic review with quantitative synthesis
Lopez-Yarto, 2012 [144]	Insufficient or inadequate data for quantitative synthesis provided
Kucukaycan, 2012 [145]	Nether a meta-analysis or systematic review with quantitative synthesis
KoKoAung, 2012 [146]	Full-text could not retrieved
Hennings, 2012 [147]	Nether a meta-analysis or systematic review with quantitative synthesis
Hackam, 2012 [148]	Insufficient or inadequate data for quantitative synthesis provided
Grzeskowiak, 2012 [149]	Nether a meta-analysis or systematic review with quantitative synthesis
Einarson, 2012 [150]	Nether a meta-analysis or systematic review with quantitative synthesis
Eom, 2012[151]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Colotto, 2012 [152]	Nether a meta-analysis or systematic review with quantitative synthesis
Bromley, 2012 [153]	Nether a meta-analysis or systematic review with quantitative synthesis
Adams, 2012 [154]	Not reporting an association of antidepressants and risk of adverse health outcomes
Gentile, 2011[155]	Nether a meta-analysis or systematic review with quantitative synthesis
Gentile, 2011 [156]	Nether a meta-analysis or systematic review with quantitative synthesis
Fenger-Gron, 2011 [157]	Nether a meta-analysis or systematic review with quantitative synthesis
Davanzo, 2011 [158]	Nether a meta-analysis or systematic review with quantitative synthesis
Dassanayake, 2011 [159]	Not reporting an association of antidepressants and risk of adverse health outcomes
Berkowitz, 2011 [160]	Nether a meta-analysis or systematic review with quantitative synthesis
Barbui, 2011[161]	Nether a meta-analysis or systematic review with quantitative synthesis

Wurst, 2010 [162]	Insufficient or inadequate data for quantitative synthesis provided
Wu, 2010 [163]	Not reporting an association of antidepressants and risk of adverse health outcomes
Van Driel, 2010 [164]	Nether a meta-analysis or systematic review with quantitative synthesis
Udechuku, 2010 [165]	Nether a meta-analysis or systematic review with quantitative synthesis
Tuccori, 2010 [166]	Nether a meta-analysis or systematic review with quantitative synthesis
Simoncelli, 2010 [167]	Nether a meta-analysis or systematic review with quantitative synthesis
Scialli, 2010 [168]	Commentary
Kemp, 2010 [169]	Not included only case-control and cohort studies
Kölch, 2010 [170]	Nether a meta-analysis or systematic review with quantitative synthesis
Kontakioti, 2010 [171]	Nether a meta-analysis or systematic review with quantitative synthesis
Einarson, 2010 [172]	Commentary
Einarson, 2010 [173]	Nether a meta-analysis or systematic review with quantitative synthesis
Berard, 2010 [174]	Commentary
Woolcott, 2009 [175]	Not included only case-control and cohort studies
Fortinguerra, 2009 [176]	Nether a meta-analysis or systematic review with quantitative synthesis
Bergemann, 2009 [177]	Nether a meta-analysis or systematic review with quantitative synthesis
Taylor, 2008 [178]	Nether a meta-analysis or systematic review with quantitative synthesis
Sterke, 2008 [179]	Nether a meta-analysis or systematic review with quantitative synthesis
O'Brien, 2008 [180]	Insufficient or inadequate data for quantitative synthesis provided
Loke, 2008 [181]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Kongkaew, 2008 [182]	Nether a meta-analysis or systematic review with quantitative synthesis
Bond, 2008 [183]	Not a meta-analysis or systematic review of observational studies
Takkouche, 2007 [184]	Insufficient or inadequate data for quantitative synthesis provided
Howard, 2007 [185]	Nether a meta-analysis or systematic review with quantitative synthesis
Hartikainen, 2007 [186]	Nether a meta-analysis or systematic review with quantitative synthesis
Bellantuono, 2007 [187]	Nether a meta-analysis or systematic review with quantitative synthesis
Bar-Oz, 2007 [188]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
Swenson, 2006 [189]	Not a meta-analysis or systematic review of observational studies
Sala, 2006 [190]	Nether a meta-analysis or systematic review with quantitative synthesis
Rahimi, 2006 [191]	Overlapping meta-analysis or systematic review of association of antidepressants and risk of adverse health outcomes
McIntyre, 2006 [192]	Nether a meta-analysis or systematic review with quantitative synthesis
McClintock, 2006 [193]	Nether a meta-analysis or systematic review with quantitative synthesis
Hall, 2006 [194]	Nether a meta-analysis or systematic review with quantitative synthesis
Lattimore, 2005 [195]	Insufficient or inadequate data for quantitative synthesis provided
Gentile, 2005 [196]	Nether a meta-analysis or systematic review with quantitative synthesis
Einarson, 2005 [197]	Insufficient or inadequate data for quantitative synthesis provided
Wen, 2004 [198]	Nether a meta-analysis or systematic review with quantitative synthesis
Weissman, 2004 [199]	Nether a meta-analysis or systematic review with quantitative synthesis
Ramasubbu, 2004 [200]	Nether a meta-analysis or systematic review with quantitative synthesis
Newman, 2004 [201]	Nether a meta-analysis or systematic review with quantitative synthesis
McIntosh, 2004 [202]	Nether a meta-analysis or systematic review with quantitative synthesis

Bailey, 2004 [203]	Insufficient or inadequate data for quantitative synthesis provided
Weinrieb, 2003 [204]	Nether a meta-analysis or systematic review with quantitative synthesis
Addis, 2000 [205]	Insufficient or inadequate data for quantitative synthesis provided
Thase, 1998 [206]	Nether a meta-analysis or systematic review with quantitative synthesis
Wilens, 1996 [207]	Nether a meta-analysis or systematic review with quantitative synthesis

eTable 2 Characteristics of meta-analyses of observational studies studying the association between antidepressants and risk of any adverse health outcome

Study (see references 38-81 in the main text)	Type of studies included	Risks of adverse health outcomes examined	Exposures	Non-exposures (comparator)	No of associations (no of included studies estimates)	Population (s)	Average of adjustments (range)	AMSTAR2
Masarwa, 2019	Case-control and cohort	Persistent pulmonary hypertension of the newborn	SSRIs+SNRIs	No SSRIs+SNRIs use	2 (19)	Pregnant women (any trimester)	9 (4-16)	Moderate
Halvorsen, 2019	Case-control and cohort	Autism spectrum disorders, attention-deficit hyperactivity disorder and mental retardation in children	SSRIs	No SSRIs use	3 (16)	Pregnant women (any trimester)	12 (4-19)	Moderate
Wang, 2018	Case-control and cohort	Dementia	SSRIs; TCAs; MAOIs	No ADs use	3 (11)	Elderly patients with various disorders	10 (8-14)	Moderate
Schweiger, 2018	Case-control and cohort	Bone mineral density	SSRIs; TCAs	No ADs use	4 (8)	Women with depressive disorders	NR	Critically Low
Khanassov, 2018	Case-control and cohort	Osteoporotic fractures	SSRIs	No SSRIs	1 (24)	General population of adults and older adults	15 (2-29)	Moderate
Jiang, 2018	Cohort	Attention-deficit hyperactivity disorder in children	Any AD	No ADs use	8 (34)	Pregnant women (any trimester)	9 (7-13)	Moderate
Gao, 2018	Cohort	Congenital malformations in infants	SSRIs	No SSRIs use	7 (37)	Pregnant women (first trimester)	5 (2-9)	Moderate
Guan, 2018	Case-control and cohort	Gestational hypertension and/or preeclampsia	SSRIs	No SSRIs use	3 (16)	Pregnant women (any trimester)	14 (10-18)	Moderate
Chappuis, 2018	Cohort	Dental implant failure	SSRIs	No SSRIs use	1 (2)	General adult population	4 (2-6)	Moderate
Na, 2018	Case-control	GI bleeding; any other type of bleeding; both GI and any other type of bleeding	Mirtazapine; Bupropion	SSRIs; No medication	5 (20)	Patients with a diagnosis of abnormal bleeding; warfarin	9 (4-16)	Moderate

Study (see references 38-81 in the main text)	Type of studies included	Risks of adverse health outcomes examined	Exposures	Non-exposures (comparator)	No of associations (no of included studies estimates)	Population (s)	Average of adjustments (range)	AMSTAR2
						users; psychiatric inpatients		
Man, 2018	Case-control and cohort	Attention-deficit hyperactivity disorder in children	Any AD	No ADs use	2 (12)	Women with prenatal or pre-conception exposure to antidepressants	8 (7-9)	Moderate
Fu, 2018	Nested case-control and case-control	Cataract risk	SSRIs; SNRIs; TCAs	No ADs use	3 (13)	Patients with medical/psychiatric diagnoses	5 (3-10)	Moderate
Eckersley, 2018	Cohort	Bleeding; mortality	SSRIs	No SSRIs use	4 (14)	Patients undergoing coronary artery bypass graft surgery	13 (9-16)	Moderate
Zhou, 2018	Case-control and cohort	Autism spectrum disorders	Any AD	No ADs use	1 (13)	Pregnant women (any trimester)	8 (3-11)	Low
Morales, 2018	Case-control and cohort	Autism spectrum disorders	Any AD	No ADs use	2 (13)	Women with pre-conception exposure to antidepressants	8 (3-11)	Moderate
Andalib, 2017	Case-control and cohort	Autism spectrum disorders	SSRIs	No SSRIs use	1 (7)	Pregnant women (any trimester)	7 (3-11)	Moderate
Zhang, 2017	Cohort	Cardiovascular-related malformations of infants; Both atrial and ventricular septal defect	SSRIs	No SSRIs use	2 (37)	Pregnant women (first trimester)	6 (0-13)	Low
Shen, 2017	Cohort	Cardiovascular-related malformations of infants	Sertraline	No sertraline or any other AD use	6 (40)	Pregnant women (first trimester)	6 (0-9)	Moderate
Laporte, 2017	Case-control and cohort	Severe bleeding at any site	SSRIs; S NRIs	No AD; No SSRI; Other AD; Neither SSRI nor NSAID	1 (44)	Patients with a diagnosis of abnormal	6 (0-17)	Low

Study (see references 38-81 in the main text)	Type of studies included	Risks of adverse health outcomes examined	Exposures	Non-exposures (comparator)	No of associations (no of included studies estimates)	Population (s)	Average of adjustments (range)	AMSTAR2
						bleeding; surgical patients		
Gao, 2017	Cohort	Congenital malformations in infants	Fluoxetine	No ADs or teratogens use	8 (38)	Pregnant women (first trimester)	5 (2-9)	Moderate
Biffi, 2017	Case-control and cohort	Onset of acute heart disease; Cerebrovascular disease	SSRIs; TCAs; Any other AD	No ADs use	4 (31)	Patients with depression	9 (0-16)	Moderate
Jiang, 2016	Nested case-control, case-control and cohort	Postpartum hemorrhage	SSRIs; Any other non-SSRIs use	No ADs use	1 (17)	Pregnant women (any trimester)	13 (7-22)	Low
Healy, 2016	Cohort	Neurodevelopmental delay/spectrum disorders	SSRI	No SSRIs	1 (17)	Pregnant women (any trimester)	NR	Moderate
Eke, 2016	Cohort	Preterm birth; respiratory distress syndrome	SSRIs	No SSRIs	3 (16)	Pregnant women (first and third trimester)	1.5 (0-5)	Moderate
Bérard, 2016	Case-control and cohort	Major cardiac malformations	Paroxetine	No paroxetine use or no any other ADs use	6 (87)	Pregnant women (first trimester)	6 (1-15)	Moderate
Undela, 2015	Case-control and cohort	Myocardial infarction	TCAs; SSRIs; Any other AD	No ADs use	1 (21)	Patients with depression	10 (2-18)	Moderate
Singh, 2015	Cohort	Perioperative bleeding outcomes and/or any cause mortality	SSRIs+SNRIs; Any other ADs	No SSRIs+SNRIs use or no any other ADs use	4 (19)	Pre-operative patients	8.6 (1-16)	Low
Jiang, 2015	Case-control and cohort	Upper GI bleeding	SSRIs+ NSAIDs + acid-suppressing drugs+ antiplatelet drugs	No ADs use only	2 (30)	Patients with various disorders with a diagnosis of UGIB	9 (0-17)	Moderate

Study (see references 38-81 in the main text)	Type of studies included	Risks of adverse health outcomes examined	Exposures	Non-exposures (comparator)	No of associations (no of included studies estimates)	Population (s)	Average of adjustments (range)	AMSTAR2
Shin, 2014	Case-control and cohort	Stroke (intracerebral hemorrhage and subarachnoid hemorrhage)	SSRIs	No SSRIs	3 (23)	Patients with depression	13 (4-31)	Low
Huang, 2014	Case-control and cohort	Low birth weight; Preterm birth	SSRIs; Any other non-SSRIs use	No ADs use	2 (43)	Pregnant women (any trimester)	NR	Moderate
Huybrechts, 2014	Case-control and cohort	Spontaneous abortion	SSIRs	No SSRIs	2 (20)	Pregnant women (early and late pregnancy)	NR	Moderate
Grigoriadis, 2014	Case-control and cohort	Pulmonary hypertension of the newborn	SSRIs	No SSRIs or no any other ADs use	1 (3)	Pregnant women with (early pregnancy)	7 (4-10)	Moderate
Oh, 2014	Case-control and cohort	Coronary heart disease	TCAs	No TCAs	1 (14)	General population of adults	NR	Moderate
Wu, 2013	Case-control and cohort	Osteoporotic fractures	TCAs	No TCAs	1 (12)	General population of older adults	12 (2-30)	Moderate
Ross, 2013	Cohort	Gestational age; APGAR score	TCAs; SSRIs; Any other AD	No ADs use	3 (42)	Pregnant women (any trimester)	3 (0-21)	Moderate
Riggin, 2013	Cohort	Congenital malformations in infants	Fluoxetine	No fluoxetine or teratogens use	2 (38)	Pregnant women (first trimester)	NR	Moderate
Grigoriadis, 2013	Case-control and cohort	Poor neonatal adaptation; Respiratory distress syndrome; Tremors	TCAs; SSRIs; SNRIs;Any other AD	No ADs use	3 (21)	Pregnant women (any trimester)	5 (4-7)	Moderate
Myles, 2013	Case-control and cohort	Major malformations in infants	Citalopram	No ADs use	2 (13)	Pregnant women (first trimester)	NR	High quality
Nikfar, 2012	Case-control and cohort	Major malformations in infants; Spontaneous abortion	SSRIs	No SSRIs	2 (28)	Pregnant women (any trimester)	NR	Low
Oderda, 2012	Case-control and cohort	Hip Fracture	Any AD	No ADs use	1 (18)	General population of older adults	5 (0-19)	Critically Low
Eom, 2012	Case-control and cohort	Breast cancer	Any AD	No ADs use	1 (18)	General population of adults	7 (1-13)	Moderate

Study (see references 38-81 in the main text)	Type of studies included	Risks of adverse health outcomes examined	Exposures	Non-exposures (comparator)	No of associations (no of included studies estimates)	Population (s)	Average of adjustments (range)	AMSTAR2
Lee, 2012	Case-control and cohort	Colon cancer	SSRIs	No SSRIs or no any other ADs use	1 (6)	General population of adults and older adults	6 (2-7)	Moderate
Cosgrove, 2011	Case-control and cohort	Breast and ovarian cancer	SSRIs; TCAs	No ADs use	2 (32)	General population of adults	NR	Low
Barbui, 2009	Case-control and cohort	Suicide attempt and completion	SSRIs	No SSRIs	3 (14)	Patients with major depressive disorders	6 (4-8)	High quality
Hemels, 2005	Cohort	Spontaneous abortion	Any AD	No ADs use	1 (11)	Pregnant women (any trimester)	NR	Moderate

AD-antidepressants, AMSTAR2 – acronym of A Measurement Tool to Assess systematic Reviews, version 2, BMD – bone mineral density, APGAR – acronym of Appearance (skin color), Pulse (heart rate), Grimace (reflex irritability), Activity (muscle tone), and Respiration, GI – gastrointestinal, NR– non reported, RCTs – randomized controlled trials, SNRIs – serotonin–norepinephrine reuptake inhibitors, SARIs – serotonin antagonist and reuptake inhibitors, SSRIs – selective serotonin reuptake inhibitors, TCAs – tricyclic antidepressants, MAOIs – monoamine oxidase inhibitors, NSAIDs – Nonsteroidal anti-inflammatory drugs, UGIB – upper gastrointestinal bleeding.

eTable 3 Suggestive evidence (Class III) for the association of antidepressant use and risk of adverse health outcomes in meta-analyses of observational studies

					Criteria used for classification of level of evidence						
Adverse health outcomes (author, year)	**Exposed/Unexposed**	**n**	**Random-effects measure, ES (95% CI)**	**Results**	**N cases/ Cohort**	**p-random effects**	**I^2 (p)**	**PI (95% CI)**	**SSE/ESB**	**LS**	**CE**
Pulmonary hypertension (pregnancy maternal exposure; Masarwa, 2019)	SSRI or SNRI users/ No SSRI or SNRI users	11	OR, 1.82 (1.31, 2.53)	Increased risk for SSRIs or SNRI	13 304/ 7 080 850	$3.6x10^{-4}$	72 (<0.000)	0.73-4.56	No/NP	Yes	III
Pulmonary hypertension (late pregnancy exposure; Masarwa, 2019)	SSRI or SNRI users/ No SSRI or SNRI users	8	OR, 2.09 (1.44, 3.02)	Increased risk for SSRIs or SNRI	12 678/ 5 979 785	$9.2x10^{-5}$	76 (<0.000)	0.77-5.68	No/No	Yes	III
Autism spectrum disorders (Halvorsen, 2019)	SSRI users/ No SSRI users	9	OR, 1.40 (1.22, 1.60)	Increased risk for SSRIs	4 334/ 1 2682 40	$9.7x10^{-7}$	15 (0.307)	1.09-1.79	No/NP	No	III
Attention-deficit hyperactivity disorder (Halvorsen, 2019)	SSRI users/ No SSRI users	5	OR, 1.39 (1.17, 1.66)	Increased risk for SSRIs	21 688/ 1 179 596	$2.3x10^{-4}$	56 (0.061)	0.82-2.37	No/NP	Yes	III
Attention-deficit hyperactivity disorder in children (Jiang, 2018)	Prenatal exposure to ADs/ No AD users	6	RR, 1.34 (1.14,1.57)	Increased risk for ADs	56 272/ 2 840 554	$3.3x10^{-4}$	79 (<0.000)	0.81–2.21	No/NP	Yes	III
Attention-deficit hyperactivity disorder in children (2+3 trimester; Jiang, 2018)	Prenatal exposure to ADs/ No AD users	5	RR, 1.37 (1.17,1.60)	Increased risk for ADs	41 564/ 2 281 198	$6.9x10^{-5}$	0 (0.754)	1.06-1.76	No/NP	Yes	III
Attention-deficit hyperactivity disorder in children (Man, 2018)	Pre-conception exposure to ADs/ Non-AD users	5	RR, 1.56 (1.24, 1.96)	Increased risk for ADs	40147/ 1864720	$1.4x10^{-4}$	58 (0.051)	0.75-3.22	No/NP	Yes	III
Cataract development (Fu, 2018)	SSRIs/non-users or no users of any other AD	6	OR, 1.12 (1.06, 1.19)	Increased risk for SSRIs	446956/ 1 955 042	$8.8x10^{-5}$	92 (<0.000)	0.92-1.37	Yes/Yes	Yes	III
Cardiovascular malformations (Zhang, 2017)	Any SSRI users/ Non-SSRI users	19	RR, 1.26 (1.13, 1.39)	Increased risk for SSRIs	75362/ 7 368 339	$2.1x10^{-5}$	54 (0.003)	0.92-1.72	No/NP	Yes	III
Both atrial and ventricular septal defect (Zhang, 2017)	Any SSRI users/ Non-SSRI users	18	RR, 1.27 (1.14, 1.42)	Increased risk for SSRIs	45247/ 10139043	$1.6x10^{-5}$	40 (0.041)	0.95-1.71	No/NP	Yes	III

Septal defects (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	8	RR, 1.38 (1.19, 1.61)	Increased risk for fluoxetine	39987/ 6438941	$2.7x10^{-5}$	0 (0.891)	1.14-1.67	No/NP	Yes	III
Cerebrovascular disease (Biffi, 2017)	SSRIs/ Non-SSRIs users	6	RR, 1.26 (1.14,1.39)	Increased risk for SSRIs	3204/ 280784	$1.0x10^{-5}$	14 (0.332)	1.02-1.55	No/No	Yes	III
Preterm birth (unadjusted estimates; Eke, 2016)	SSRIs/ Non-SSRIs users	8	OR, 1.59 (1.31, 1.92)	Increased risk for SSRIs	69 912/ 1 307 761	$2.0x10^{-5}$	92 (<0.000)	0.91-2.78	Yes/Yes	Yes	III
Respiratory distress syndrome (Eke, 2016)	SSRIs/ Non-SSRIs users	5	OR,1.33 (1.14,1.55)	Increased risk for SSRIs	19032/ 1269710	$2.6x10^{-4}$	83 (<0.000)	0.83-2.12	Yes/Yes	Yes	III
Major malformations (Bérard, 2016)	Paroxetine/ No paroxetine use	15	OR, 1.23 (1.10, 1.38)	Increased risk for paroxetine	26752/ 2 169 318	$3.8x10^{-4}$	3 (0.424)	1.06-1.43	No/NP	No	III
Cardiac malformations (Bérard, 2016)	Paroxetine/ No paroxetine use	18	OR, 1.28 (1.11,1.47)	Increased risk for paroxetine	75953/ 5109058	$2.3x10^{-5}$	0 (0.653)	1.09-1.49	No/NP	No	III
Requirement of blood/RBC transfusion (Singh, 2015)	SSRIs+SNRIs/ Non SADs users	7	OR, 1.19 (1.09, 1.30)	Increased risk for SADs	79775/ 556120	$1.0x10^{-4}$	36 (0.155)	0.97-1.46	No/No	Yes	III
Upper gastrointestinal bleeding (Jiang, 2015)	SSRIs/ Non-SSRIs users	8	1.95 (1.44, 1.93)	Increased risk for SSRIs	32830/ 241266	$1.2x10^{-5}$	90 (<0.000)	0.70-5.38	No/NP	Yes	III
Low birth weight (Huang, 2014)	Any AD users/ Non-AD users	15	RR, 1.44 (1.21, 1.70)	Increased risk for ADs	20190/ 3001141	$2.8x10^{-5}$	61 (0.001)	0.88-2.32	No/NP	Yes	III
Preterm birth during late pregnancy (Huybrechts, 2015)	Any AD users/ Non-AD users	12	OR, 1.98 (1.65, 2.37)	Increased risk for ADs	NR/ 1891969	$2.4X10^{-13}$	83 (<0.000)	1.09-2.37	Yes/NP	Yes	III
Gestational age (Ross, 2013)	Any AD users/ Non-AD users	16	SMD, -0.23 (-0.33,-0.12)	Increased risk for ADs	3419/ 60644	$3.9x10^{-5}$	71 (<0.000)	-0.81, 0.36	No/Yes	Yes	III

RBC–red blood cells, AD– antidepressants, TCAs – tricyclic antidepressants, SSRIs – selective serotonin reuptake inhibitors, SNRIs – serotonin–norepinephrine reuptake inhibitors, n – number of included studies per association, ES – effect size, N – number of cases, I^2 –heterogeneity, PI – prediction interval, CI – confidence interval, SSE – small-study effect, ESB –excess significance bias, LS – largest study with significant effect, CE – class of evidence, OR – odds ratio, RR – relative risk, SMD – standardized mean difference, NA– not applicable, NP – not pertinent because the number of observed studies is less than the expected.

eTable 4 Weak evidence (Class IV) for the association of antidepressant use and risk of adverse health outcomes in meta-analyses of observational studies

					Criteria used for classification of level of evidence						
Adverse health outcomes (author, year)	**Exposed/Unexposed**	**n**	**Random-effects measure, ES (95% CI)**	**Results**	**N cases/ Cohort**	**p-random effects**	**I^2 (p)**	**PI (95% CI)**	**SSE/ESB**	**LS**	**CE**
Mental retardation (Halvorsen, 2019)	SSRI users/ No SSRI users	2	HR, 1.41 (1.03, 1.91)	Increased risk for SSRIs	NR/ NR	0.030	0 (0.718)	NA	NA/NA	No	IV
Dementia (Wang, 2018)	SSRI users/ No SSRI users	5	RR, 1.75 (1.03, 2.96)	Increased risk for SSRIs	NR / 53955	0.037	98 (<0.000)	0.23–13.49	No/NA	Yes	IV
Dementia (Wang, 2018)	TCA users/ No SSRI users	4	RR, 2.13 (1.43, 3.18)	Increased risk for TCAs	NR/ 22768	$2.1x10^{-4}$	96 (<0.000)	0.34-13.54	No/NA	Yes	IV
Dementia (Wang, 2018)	MAOI users/ No MAOI users	2	RR, 2.79 (1.09, 7.17)	Increased risk for MAOIs	NR/ 12 209	0.033	80 (0.025)	NA	NA/NA	Yes	IV
Attention-deficit hyperactivity disorder (first trimester; Jiang, 2018)	Prenatal exposure to ADs/ No AD users	4	RR, 1.28 (1.00,1.64)	Increased risk for ADs	55988/ 293431	0.047	91 (<0.000)	0.41–4.01	No/NP	Yes	IV
Attention-deficit hyperactivity disorder in children (Jiang, 2018)	Maternal psychiatric disorder without exposure versus no exposure	3	RR, 1.34 (1.08,1.67)	Increased risk for ADs	NR/ NR	0.007	60 (0.083)	0.13-13.88	No/NA	Yes	IV
Attention-deficit hyperactivity disorder in children (Jiang, 2018)	SSRIs / Non-SSRIs users	5	RR, 1.35 (1.13,1.61)	Increased risk for ADs	NR/ NR	0.001	86 (<0.000)	0.72-2.51	No/NA	Yes	IV
Attention-deficit hyperactivity disorder in children (Jiang, 2018)	Non-SSRI antidepressant use/ Non-AD users	6	RR, 1.49 (1.22,1.83)	Increased risk for ADs	NR/ NR	$1.2x10^{-4}$	0 (0.790)	1.12-1.99	No/NA	Yes	IV
Gestational hypertension or preeclampsia (Guan, 2018)	SSRI users/ No SSRI users	7	RR, 1.21 (1.05, 1.40)	Increased risk for SSRIs	12097/ 1108261	0.007	71 (0.002)	0.81-1.82	Yes/Yes	No	IV
Atrial septal defects (Gao, 2018)	Any SSRI users/ Non-SSRI users	7	RR, 1.83 (1.22, 2.72)	Increased risk for SSRIs	6366/ 2560254	0.003	72 (0.002)	0.53-6.31	No/Yes	No	IV
Septal defects (Gao, 2018)	Any SSRI users/ Non-SSRI users	6	RR, 1.38 (1.00, 1.91)	Increased risk for SSRIs	8029/ 2039943	0.050	67 (0.009)	0.50-3.80	No/NP	Yes	IV
Right ventricular outflow tract defects	Any SSRI users/ Non-SSRI users	4	RR, 1.38 (1.09, 1.75)	Increased risk for SSRIs	4307/ 2360018	0.007	33 (0.214)	0.63-3.03	No/NP	Yes	IV

(Gao, 2018)											
Gestational hypertension (Guan, 2018)	SSRI users/ No SSRI users	4	RR, 1.14 (1.00-1.30)	Increased risk for SSRIs	4370/ 91 282	0.048	6 (0.365)	0.79-1.64	No/NP	No	IV
Dental implant failure (Chappuis, 2018)	SSRI users/ No SSRI users	2	OR, 2.02 (1.42, 2.88)	Increased risk for SSRIs	341/ 5 332	$9.8x10^{-5}$	0 (0.770)	NA	NA/No	Yes	IV
GI bleeding (Na, 2018)	Mirtazapine/ no medication	4	OR, 1.17 (1.01,1.37)	Increased risk for mirtazapine	2116/ 59571	0.043	0 (0.593)	0.83-1.65	No/NP	No	IV
Cataract development (Fu, 2018)	SNRIs/ non-users or no users of any other AD	4	OR, 1.13 (1.04, 1.24)	Increased risk for SNRIs	239390/ 646822	0.006	68 (0.026)	0.79-1.63	Yes/No	Yes	IV
Autism spectrum disorders (Zhou, 2018)	Any AD users/ Non-AD users	13	OR, 1.28 (1.07, 1.53)	Increased risk for SSRIs	26695/ 2699647	0.007	62 (0.002)	0.72-2.26	No/NP	No	IV
Cardiovascular malformations (Shen, 2017)	Sertraline users/Non-sertraline users	12	OR, 1.36 (1.06, 1.74)	Increased risk for sertraline	57493/ 6468241	0.015	64 (0.001)	0.66-2.79	No/NP	Yes	IV
Non-septal defects (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	9	RR, 1.39 (1.12, 1.73)	Increased risk for fluoxetine	14240/ 10822445	0.003	7 (0.374)	0.98-1.97	No/NP	Yes	IV
Preterm birth (adjusted) (Eke, 2016)	SSRIs/ Non-SSRIs users	3	OR, 1.24 (1.09, 1.41)	Increased risk for SSRIs	66652/ 967061	0.001	73 (0.026)	0.31-4.96	No/NP	Yes	IV
Major malformations (Bérard, 2016)	Paroxetine/ No any other SSRIs use	14	OR, 1.19 (1.06, 1.34)	Increased risk for paroxetine	82965/ 4052678	0.003	0 (0.712)	1.05-1.35	No/NP	No	IV
Major malformations (Bérard, 2016)	Paroxetine/ No any other ADs use	10	OR, 1.19 (1.05, 1.35)	Increased risk for paroxetine	100735/ 5766472	0.008	0 (0.578)	1.02-1.38	No/NP	No	IV
Cardiac malformations (Bérard, 2016)	Paroxetine/No any other SSRIs use	17	OR, 1.27 (1.10,1.47)	Increased risk for paroxetine	75138/ 5103306	0.001	0 (0.596)	1.08-1.49	No/NP	No	IV
Cardiac malformations (Bérard, 2016)	Paroxetine/ No any other ADs use	13	OR, 1.23 (1.06, 1.43)	Increased risk for paroxetine	102941/ 6435313	0.006	1 (0.436)	1.03-1.48	No/NP	No	IV
Autistic Spectrum or related Disorders (Healy, 2016)	SSRIs / Non-SSRIs users	17	OR, 1.96 (1.33, 2.88)	Increased risk for SSRIs	23641/ 2321521	0.001	91 (<0.000)	0.42-9.02	No/NP	Yes	IV
Ischemic stroke (Shin, 2014)	SSRIs / Non-SSRIs users	6	OR, 1.48 (1.08, 2.02)	Increased risk for SSRIs	11080/ 724936	0.015	84 (<0.000)	0.50-4.35	No/No	No	IV

Hemorrhagic stroke (Shin, 2014)	SSRIs / Non-SSRIs users	11	OR, 1.32 (1.02, 1.71)	Increased risk for SSRIs	11513/ 399305	0.033	75 (<0.000)	0.57-3.07	No/NP	Yes	IV
All types of stroke (Shin, 2014)	SSRIs / Non-SSRIs users	6	OR, 1.40 (1.09, 1.80)	Increased risk for SSRIs	3519/ 223986	0.008	93 (<0.000)	0.57-3.44	No/Yes	Yes	IV
Coronary heart disease (Oh, 2014)	TCAs/ Non-TCAs users	14	OR, 1.51 (1.07, 2.12)	Increased risk for TCAs	6443/ 347750	0.019	97 (<0.000)	0.41-5.56	No/NP	Yes	IV
Apgar score at 1 minute (Ross, 2013)	Any AD users/ Non-AD users	11	SMD,-0.19 (-0.30,-0.08)	Increased risk for ADs	714/ 1534	0.001	7 (0.376)	-0.72, 0.34	No/NP	No	IV
Cardiovascular malformations (Riggin, 2013)	Fluoxetine/ Non fluoxetine or teratogens users	16	OR, 1.60 (1.32, 1.95)	Increased risk for fluoxetine	35702/ 3401555	$2.4x10^{-6}$	1 (0.441)	1.27-2.02	No/NP	No	IV
Poor neonatal adaptation (Grigoriadis, 2013)	Any AD users/ Non-AD users	8	OR, 5.06 (3.25, 7.89)	Increased risk for ADs	75/ 986	$7.8x10^{-13}$	0 (0.617)	2.91-8.81	No/No	Yes	IV
Respiratory distress syndrome (Grigoriadis, 2013)	Any AD users/ No AD users	9	OR, 2.20 (1.81, 2.66)	Increased risk for ADs	623/ 583525	$1.3x10^{-15}$	38 (0.115)	1.43-3.37	Yes/Yes	Yes	IV
Tremors (Grigoriadis, 2013)	Any AD users/ Non-AD users	4	OR, 7.90 (3.33, 18.73)	Increased risk for ADs	60/ 482	$2.7x10^{-6}$	45 (0.144)	0.35-177.44	No/Yes	Yes	IV
Major malformations (Nikfar, 2013)	SSRIs / Non-SSRIs users	21	OR, 1.23 (1.08, 1.41)	Increased risk for SSRIs	60753/ 1761861	0.002	25 (0.146)	0.91-1.68	Yes/No	No	IV
Spontaneous abortion (Nikfar, 2013)	SSRIs / Non-SSRIs users	7	OR, 1.85 (1.41, 2.42)	Increased risk for SSRIs	376/ 4140	$9.6x10^{-6}$	3 (0.403)	1.25-2.74	No/No	No	IV
Breast and ovarian cancer (Cosgrove, 2011)	SSRIs / Non-SSRIs users	16	OR, 1.05 (1.01, 1.10)	Increased risk for SSRIs	46796/ 1059784	0.010	15 (0.287)	0.98-1.14	Yes/No	No	IV
Suicide attempt and completion in adults (Barbui, 2009)	SSRIs / Non-SSRIs users	2	OR, 0.47 (0.27, 0.80)	Decreased risk for SSRIs	107/ 178529	$4.1x10^{-9}$	0 (0.555)	NA	NA/NP	No	IV
Spontaneous abortion (Hemels, 2005)	Any AD users/ Non-AD users	11	OR, 1.46 (1.19, 1.79)	Increased risk for ADs	373/ 3194	$2.8x10^{-3}$	0 (0.981)	1.15-1.85	No/NP	No	IV

AD–antidepressants, APGAR – backronym of Appearance (skin color), Pulse (heart rate), Grimace (reflex irritability), Activity (muscle tone), and Respiration, TCAs – tricyclic antidepressants, SSRIs – selective serotonin reuptake inhibitors, SNRIs – serotonin–norepinephrine reuptake inhibitors, n – number of included studies per association, ES – effect size, N – number of cases, I^2 –heterogeneity, PI – prediction interval, CI – confidence interval, SSE – small-study effect, ESB –excess significance bias, LS – largest study with

significant effect, CE – class of evidence, OR – odds ratio, RR – relative risk, NA– not applicable, NP – not pertinent because the number of observed studies is less than the expected.

eTable 5 No evidence (Non-significant associations, p>0.05) for the association of antidepressant use and risk of adverse health outcomes in meta-analyses of observational studies

					Criteria used for classification of level of evidence						
Adverse health outcomes (author, year)	**Exposed/ Unexposed**	**n**	**Random-effect measure, ES (95% CI)**	**Results**	**N cases/ Cohort**	**p- random effects**	**I^2 (p)**	**PI (95% CI)**	**SSE/ESB**	**LS**	**CE**
Major congenital anomalies (Gao, 2018)	Maternal psychiatric disorder with SSRI exposure versus no exposure	4	RR, 1.03 (0.95, 1.13)	No evidence of risk	63383/ 1851983	0.439	3 (0.380)	0.85-2.26	No/No	No	NS
Cardiovascular malformations (Gao, 2018)	Maternal psychiatric disorder with SSRI exposure versus no exposure	6	RR, 1.06 (0.89, 1.26)	No evidence of risk	22192/ 2685027	0.489	34 (0.182)	0.71-1.60	No/NP	No	NS
Left ventricular outflow tract defects (Gao, 2018)	SSRIs / Non-SSRIs users	3	RR, 1.08 (0.81, 1.44)	No evidence of risk	3117/ 1410514	0.616	0 (0.892)	0.17-6.99	No/NP	No	NS
Ventricular septal defect (Gao, 2018)	SSRIs / Non-SSRIs users	8	RR, 1.10 (0.93, 1.29)	No evidence of risk	13647/ 3509759	0.232	36 (0.140)	0.76-1.60	NA/NP	Yes	NS
BMD Lumbar Spine (Schweiger, 2018)	SSRIs / Non-SSRIs users	2	SMD, -0.03 (-0.43, 0.38)	No evidence of risk	NR/ 2100	0.897	71 (0.065)	NA	NA/No	Yes	NS
BMD Femoral Neck (Schweiger, 2018)	TCAs / Non-TCAs users	2	SMD, 0.02 (-0.14, 0.18)	No evidence of risk	NR/ 3851	0.786	0 (0.545)	NA	NA/NP	No	NS
BMD Total Hip (Schweiger, 2018)	SSRIs / Non-SSRIs users	2	SMD, 0.10 (-0.38, 0.59)	No evidence of risk	NR/ 4694	0.677	98 (<0.000)	NA	NA/No	Yes	NS
BMD Total Hip (Schweiger, 2018)	TCAs / Non-TCAs users	2	SMD, 0.03 (-0.12, 0.17)	No evidence of risk	NR/ 4694	0.719	0 (0.644)	NA	NA/NP	No	NS
Attention-deficit hyperactivity disorder in children (Jiang, 2018)	Exposure versus maternal psychiatric disorder without exposure	2	RR, 0.96 (0.76,1.20)	No evidence of risk	NR/ NR	0.714	0 (0.524)	NA	NA/NA	No	NS
Attention-deficit hyperactivity disorder in children (Jiang, 2018)	Sibling matched	3	RR, 0.88 (0.70,1.11)	No evidence of risk	NR/ NR	0.293	0 (0.486)	0.20-3.99	Yes/NA	No	NS

Preeclampsia (Guan, 2018)	SSRI users/ No SSRI users	5	RR, 1.32 (0.98-1.78)	No evidence of risk	7 727/ 201 181	0.071	83 (<0.000)	0.47-3.70	No/No	No	NS
GI bleeding (Na, 2018)	Mirtazapine/SSRIs	4	OR, 1.03 (0.89,1.19)	No evidence of risk	2116/ 59571	0.689	0 (0.806)	0.75 -1.41	No/NP	No	NS
Any other type of bleeding (Na, 2018)	Bupropion/SSRIs	3	OR, 0.90 (0.68,1.18)	No evidence of risk	1228/ 16223	0.443	0 (0.886)	0.15-5.24	No/NP	No	NS
Both GI and any other type of bleeding (Na, 2018)	Mirtazapine/SSRIs	5	OR, 0.98 (0.98,1.14)	No evidence of risk	2751/ 63545	0.766	6 (0.371)	0.77-1.25	No/NP	No	NS
Both GI and any other type of bleeding (Na, 2018)	Mirtazapine/ no medication	4	OR, 1.12 (0.97,1.29)	No evidence of risk	2116/ 59571	0.131	0 (0.619)	0.81-1.53	No/NP	No	NS
Transfusion of FFP (Eckersley, 2018)	SSRIs users/ Non-SSRI users	3	OR, 0.96 (0.74,1.24)	No evidence of risk	8510/ 139711	0.754	60 (0.083)	0.06-14.93	No/NP	No	NS
Transfusion of platelets (Eckersley, 2018)	SSRIs users/ Non-SSRI users	3	OR, 0.93 (0.78, 1.11)	No evidence of risk	4424/ 139711	0.418	5 (0.349)	0.26-3.28	No/NP	No	NS
Re-operation for bleeding (Eckersley, 2018)	SSRIs users/ Non-SSRI users	3	OR, 1.07 (0.66, 1.74)	No evidence of risk	446/ 11955	0.783	0 (0.964)	0.05-25.20	No/NP	No	NS
Thirty-day mortality (Eckersley, 2018)	SSRIs users/ Non-SSRI users	5	OR, 1.03 (0.91, 1.16)	No evidence of risk	6668/ 270103	0.664	0 (0.814)	0.84-1.26	No/NP	No	NS
Autism spectrum disorders (Morales, 2018)	Any AD users/ Non-AD users with a history of affective disorder	6	RR, 1.18 (0.91, 1.52)	No evidence of risk	7780/ 1052964	0.192	51 (0.069)	0.58 -2.40	No/NP	No	NS
Nervous system (Shen, 2017)	Sertaline users/Non-sertraline users	6	OR, 1.43 (0.88, 2.32)	No evidence of risk	416/ 1975394	0.149	0 (0.976)	0.72-2.84	No/NP	No	NS

Digestive system (Shen, 2017)	Sertaline users/Non-sertraline users	5	OR, 1.23 (0.76, 1.98)	No evidence of risk	720/ 1657603	0.407	0 (0.805)	0.56-2.68	No/NP	No	NS
Eye, ear, face and neck (Shen, 2017)	Sertaline users/Non-sertraline users	4	OR, 1.08 (0.33, 3.55)	No evidence of risk	316/ 1839470	0.902	32 (0.219)	0.02-56.42	No/NP	No	NS
Urogenital system (Shen, 2017)	Sertaline users/Non-sertraline users	8	OR, 1.03 (0.73,1.46)	No evidence of risk	1638/ 1676096	0.869	0 (0.755)	0.67-1.59	Yes/NP	No	NS
Musculoskeletal system (Shen, 2017)	Sertaline users/Non-sertraline users	5	OR, 0.97 (0.69, 1.36)	No evidence of risk	1694/ 1657603	0.861	0 (0.723)	0.56-1.68	No/NP	No	NS
Nervous system malformations (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	3	RR, 1.37 (0.83, 2.25)	No evidence of risk	2925/ 1817322	0.219	0 (0.526)	0.05-34.60	No/NP	No	NS
Eye malformations (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	3	RR, 1.30 (0.53, 3.17)	No evidence of risk	2585/ 1270645	0.564	0 (0.399)	0.00-420.44	No/NP	No	NS
Urogenital malformations (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	5	RR, 1.02 (0.65, 1.59)	No evidence of risk	4244/ 2262620	0.932	39 (0.159)	0.00-3.50	No/NP	Yes	NS
Digestive malformations (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	3	RR, 1.08 (0.60, 1.96)	No evidence of risk	2019/ 1816416	0.800	0 (0.861)	0.02-51.29	No/NP	No	NS
Respiratory malformations (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	3	RR, 1.38 (0.69, 2.78)	No evidence of risk	472/ 1814869	0.361	0 (0.670)	0.02-127.68	No/NP	No	NS
Musculoskeletal malformations (Gao, 2017)	Fluoxetine/ No ADs or teratogens use	4	RR, 0.82 (0.54, 1.22)	No evidence of risk	1474/ 1910723	0.322	0 (0.726)	0.34-1.98	Yes/NP	No	NS

Acute heart disease (Biffi, 2017)	Any AD users/ Non-AD users	7	RR, 1.35 (0.91, 2.02)	No evidence of risk	65331/ 818933	0.138	92 (<0.000)	0.35-5.19	No/NP	Yes	NS
Acute heart disease (Biffi, 2017)	SSRIs/ Non-SSRIs users	14	RR, 1.00 (0.83,1.22)	No evidence of risk	89421/ 818337	0.961	85 (<0.000)	0.53-1.90	Yes/NP	Yes	NS
Cerebrovascular disease (Biffi, 2017)	TCAs/ Non-TCAs users	4	RR, 1.06 (0.96, 1.17)	No evidence of risk	7325/ 278749	0.239	0 (0.745)	0.85-1.32	No/NP	No	NS
Preterm birth (Huybrechts, 2015)	Any AD users in early pregnancy/ Non-AD users	8	OR, 1.15 (0.96, 1.38)	No evidence of risk	NR/ 1371456	0.127	85 (<0.000)	0.64-2.07	No/NP	Yes	NS
Myocardial infarction (Undela, 2015)	Any AD users/ Non-AD users	21	RR, 1.03 (0.88, 1.22)	No evidence of risk	220362/ 1793877	0.687	98 (<0.000)	0.51-2.08	No/NP	Yes	NS
Requirement of reoperation for bleeding complication (Singh, 2015)	SSRIs+SNRIs/ Non SADs users	4	OR, 1.48 (0.84, 2.62)	No evidence of risk	676/ 26743	0.176	54 (0.089)	0.17-13.06	No/NP	Yes	NS
Mortality-any cause (Singh, 2015)	SSRIs+SNRIs/ Non SADs users	5	OR, 1.15 (0.86, 1.53)	No evidence of risk	79683/ 554079	0.343	76 (0.002)	0.46-2.88	No/No	Yes	NS
Requirement of RBC transfusion (Singh, 2015)	Any other AD users/ Non-any other AD users	3	OR, 1.03 (0.74, 1.43)	No evidence of risk	216/ 5495	0.874	0 (0.790)	0.12-8.88	No/NP	No	NS
Pulmonary hypertension of the newborn (Grigoriadis, 2014)	SSRIs early in pregnancy/ Non-SSRIs users	3	OR,1.22 (0.58, 2.60)	No evidence of risk	49/ 13017	0.600	78 (0.010)	0.00-7225.40	No/NP	No	NS
Major malformations (Riggin, 2013)	Fluoxetine/ No fluoxetine or teratogens use	22	OR,1.12 (0.98, 1.28)	No evidence of risk	163333/ 4576977	0.109	29 (0.106)	0.78-1.61	No/NP	No	NS
Cardiovascular malformations (Myles, 2013)	Citalopram during first trimester / Non-AD users	6	OR, 0.99 (0.75, 1.30)	No evidence of risk	NR/NR	0.459	34 (0.183)	0.51-1.92	No/NA	No	NS

Major malformations (Myles, 2013)	Citalopram during first trimester Non-AD users	7	OR, 1.04 (0.92, 1.17	No evidence of risk	NR/NR	0.254	0 (0.858)	0.89-1.21	No/NA	No	NS
Breast cancer (Eom, 2012)	Any AD users/ Non-AD users	18	OR,1.02 (0.96, 1.08)	No evidence of risk	65313/ 739891	0.574	36 (0.063)	0.87-1.18	Yes/NP	No	NS
Colon cancer (Lee, 2012)	SSRIs / Non-SSRIs users or any other ADs	6	OR, 0.89 (0.79, 1.01)	No evidence of risk	11710/ 978578	0.071	41 (0.131)	0.66-1.21	No/No	No	NS
Breast and ovarian cancer (Cosgrove, 2011)	TCAs/Non-TCAs	16	OR, 1.03 (0.98,1.09)	No evidence of risk	37923/ 426545	0.251	47 (0.021)	0.88-1.22	No/NP	No	NS

GI – gastrointestinal, RBC–red blood cells, FFP– fresh frozen plasma, BMD – bone mineral density, AD– antidepressants, TCAs – tricyclic antidepressants, SSRIs – selective serotonin reuptake inhibitors, SNRIs – serotonin–norepinephrine reuptake inhibitors, SADs– serotoninergic antidepressants, n – number of included studies per association, ES – effect size, N – number of cases, I^2 –heterogeneity, PI – prediction interval, CI – confidence interval, SSE – small-study effect, ESB –excess significance bias, LS – largest study with significant effect, CE – class of evidence, CES= OR – odds ratio, RR – relative risk, HR– hazard ratio, SMD – standardized mean difference, NA– not applicable, NP – not pertinent because the number of observed studies is less than the expected.

Supplementary methods

Selection between overlapping meta-analysis

At full-text assessment, we extracted relevant information to define antidepressants exposure, inclusion criteria for the population of interest and outcome definition of each meta-analysis. When two or more meta-analyses focused on the same combination of exposure, population, and outcome we selected only the meta-analysis that included the largest data set and sufficient individual data for statistical analysis.[208] We also examined whether the main reported conclusions were concordant regarding the direction and the significance level of the association.[2] If the results were concordant, then again, we selected the one that included the largest data set and sufficient individual data for statistical analysis.[208]If two or more meta-analyses focused on the same combination of exposure, population, and outcome, but included a different set of primary studies (for example, different set of cohort studies but the same set of case-control studies and vice versa, or only cohort studies) then we kept both or all. If two or more meta-analyses focused on the same combination of exposure, population, and outcome and included exactly the same number and set of included studies then we kept the most recent one.[209] We adopted this procedure not only to avoid overlapping data sets as much as possible, but also not to miss as much any valuable information. We also examined the concordance between selected and non-selected meta-analyses by sensitivity analysis limited to non-selected associations due to overlap (eTable 6).[210]

Quality assessment

AMSTAR 2 [211] assesses whether included meta-analyses clearly defined the research question and inclusion criteria, mentioned an a-priori protocol, explained inclusion criteria, conducted a comprehensive literature search, screened literature and extracted data in duplicate, provided a list of excluded studies with reason for exclusion, described included studies in detail, assessed risk of bias of included studies, reported on the source of funding, used appropriate statistical methods, accounted for risk of bias for instance with sensitivity analyses, considered risk of bias when interpreting results, explained and discussed any heterogeneity in results, assessed and discussed

publication bias, reported any potential conflict of interest. Based on the above listed items, AMSTAR 2 defines a systematic review's quality as high, moderate, low, or critically low. Compared with AMSTAR, AMSTAR 2 also assesses the quality of the studies included in a meta-analysis, without limiting the quality assessment to the technical aspects of the meta-analysis itself. Additionally, compared to ROBIS, AMSTAR has much better agreement among raters.[212]

Grading method

We assessed the credibility of the evidence using established criteria published in several umbrella reviews.[208,209,210] Specifically, associations had the strongest validity and were not suggestive of bias (Class I: convincing) whenever they met all the following criteria: had >1000 cases; had p-value $<10^{-6}$ based on random-effects meta-analysis; had no evidence of small-study effects and excess significance; had 95% prediction interval (PI) that excluded the null value; the largest study had a nominally significant effect ($p<0.05$); and had low or moderate between-study heterogeneity (I^2 <50%). Highly suggestive evidence (Class II) required >1000 cases; had p-value $<10^{-6}$ based on random-effects meta-analysis; and the largest study had a nominally significant effect ($p<0.05$). Suggestive evidence (Class III) criteria required only >1000 cases and had p-value $<10^{-3}$ based on random-effects meta-analysis. Weak evidence (Class IV) criteria required only all other remained associations with a p-value ≤0.05. These criteria have been proven to provide a systematic and transparent judgment of the methodological flaws that can occur in various meta-analyses. It is well known, that heterogeneity, publication bias, small-study effects, selective reporting, and excess of significant bias in the published meta-analyses can contribute to biased results of a meta-analyses. Thus, this method appears to be more objective than other quality grading methods because it uses several statistical tests to assess different type of bias and it can work for many types of research questions.[213] Notably, an empirical evaluation of different grading approaches concluded that agreement was poor and that all methods had important shortcomings.[214]

Supplementary results

Sensitivity analysis results of convincing and highly suggestive evidence associations from the main analysis

Cohort studies (both prospective and retrospective)

A sensitivity analysis limited to cohort studies showed that none of the associations within class I retained the same rank (Table 3). However, this analysis showed that six associations were supported by highly suggestive evidence (Table 3). These included the increased risk of autism during pregnancy, osteoporotic fractures, pre-term birth and lower APGAR scores at 5 minutes (antidepressants during pregnancy), and suicide attempt/completion in children and adolescents, as well as the decreased risk of suicide attempt/completion in adults and older adults.

The associations between antidepressants and attention-deficit hyperactivity disorder in children, postpartum haemorrhage, and osteoporotic fractures (TCAs) were downgraded to suggestive evidence, while the associations between antidepressants and ASD during pre-pregnancy, severe bleeding, upper gastrointestinal bleeding, and hip fracture were downgraded to weak evidence.

Prospective cohort studies

A sensitivity analysis limited to prospective cohort studies showed that none of the associations within class I retained the same rank (Table 3). The most important change was for highly suggestive associations, with one being upgraded to convincing evidence (preterm birth related to any antidepressant use), while all other were downgraded to lower ranks of evidence. More analytically, the associations between antidepressants and attention-deficit hyperactivity disorder in children, and postpartum haemorrhage were downgraded to suggestive evidence, while the associations with severe bleeding and Apgar score at 5 minutes were downgraded to weak evidence. Finally, the association with autism during pre-pregnancy turned into non-significant.

Studies adjusted for multiple covariates

When the sensitivity analysis was limited to studies adjusted for multiple potential confounders beyond age and sex (as described in eTable 7 in the Supplement), the association with suicide risk

in children and adolescents, the association between any antidepressant and ASD during pre-pregnancy remained at convincing evidence, while five more associations remained at highly suggestive evidence as in the main analysis (Table 5). These included, increased risk of attention-deficit hyperactivity disorder in children, osteoporotic fractures (SSRIs and TCAs), hip fracture (any antidepressant), and upper gastrointestinal bleeding. The positive associations with cataract development, severe bleeding, and postpartum haemorrhage were downgraded to suggestive evidence as well as the protective association with suicide risk in adults, whereas the association with preterm birth, and Apgar score at 5 minutes were downgraded to weak evidence. Finally, the association with autism during pregnancy included only unadjusted estimates and excluded from this analysis.

Confounding by indication

This analysis included only adjusted studies that were controlled/matched for a psychiatric condition as depicted in eTable 7 in the Supplement. This analysis showed that none of the associations within class I retained the same rank (Table 3). The association with autism during pre-pregnancy was downgraded to highly suggestive, while the association with suicide attempt/completion in children and adolescents was downgraded to weak (Table 4 in the main text). Two more associations, i.e., osteoporotic fractures (SSRIs and TCAs) remained at highly suggestive evidence as in main analysis (Table 3). The associations with attention-deficit hyperactivity disorder in children, postpartum haemorrhage, and the protective association with suicide risk in adults, were downgraded to suggestive evidence, while the association with preterm birth was downgraded to weak evidence.

High-quality primary studies

This analysis limited to high-quality primary studies that had a Newcastle-Ottawa Scale (NOS) score bigger than seven (or defined as such by using other instruments) as reported from the original meta-analyses' authors. This analysis showed that the three associations within class I retained the same rank (Table 3). These included the increased risk of autism before and during

pregnancy, and suicide attempt and completion in children and adolescents. Seven more associations remained at highly suggestive evidence as in main analysis (Table 3). These included the attention-deficit hyperactivity disorder in children, osteoporotic fractures (SSRIs and TCAs), hip fracture (any antidepressant), postpartum haemorrhage, preterm birth, and the protective association with suicide risk in adults. The remaining associations with cataract development, severe bleeding, upper gastrointestinal bleeding, and Apgar score at 5 minutes were downgraded to weak evidence.

Classes of antidepressants

A sensitivity analysis limited to SSRIs showed that the associations with increased suicide risk in children and adolescents and autism during pregnancy remained convincing, while another one was upgraded to convincing evidence (lower APGAR scores at 5 minutes). Three more associations were supported by highly suggestive evidence (Table 3). These included the osteoporotic fractures, preterm birth, and the protective association with suicide risk in adults.

When the sensitivity analysis was limited to TCAs, two associations remained at highly suggestive evidence i.e., cataract development and osteoporotic fractures.

The analysis limited to other or mixed antidepressants showed that the association between any antidepressant and autism during pre-pregnancy remained convincing, one association was upgraded to convincing evidence (preterm birth), while one was downgraded to suggestive evidence (attention-deficit hyperactivity disorder in children). Another one turned into non-significant, i.e, APGAR scores at 5 minutes. Finally, three other associations remained at highly suggestive evidence (Table3). These included severe bleeding, postpartum haemorrhage, and upper gastrointestinal bleeding.

Studies located in Europe

When the sensitivity analysis was limited to studies located in Europe, the association between SSRIs and autism during pregnancy remained at convincing evidence (Table3), while the association with suicide attempt/completion in children and adolescents was downgraded to weak

evidence. Five associations remained at highly suggestive evidence (upper gastrointestinal bleeding, preterm birth, osteoporotic fractures (SSRIs and TCAs), and hip fractures (either TCAs or SSRIs). The association with severe bleeding and the protective association with suicide risk in adults were downgraded to suggestive evidence, while the associations with attention-deficit hyperactivity disorder in children and Apgar score at 5 minutes were downgraded to weak evidence.

Studies located in North America

When the sensitivity analysis was limited to studies located in North America i.e.., USA and Canada, none of the associations within class I retained the same rank (Table 3). Four more associations i.e., osteoporotic fractures (SSRIs and TCAs), hip fractures (either TCAs or SSRIs), and preterm birth remained at highly suggestive evidence as in main analysis (Table 4 in the main text). The associations with autism during pregnancy and severe bleeding were downgraded to suggestive evidence, while the associations with autism before pregnancy, suicide attempt/completion in children and adolescents, attention-deficit hyperactivity disorder in children, postpartum haemorrhage, upper gastrointestinal bleeding, Apgar score at 5 minutes, and the protective association with suicide risk in adults were downgraded to weak evidence.

Studies located in other regions

When the sensitivity analysis was limited to studies located in other regions, none of the associations within class I and II retained the same rank (Table3). The associations with postpartum haemorrhage, upper gastrointestinal bleeding, preterm birth, and hip fracture (either TCAs or SSRIs) were downgraded to weak evidence, while the association with severe bleeding turned into non-significant. For the remaining associations within Class I and II there were no available data.

Sensitivity analysis results of non-selected meta-analyses due to overlap

The results from this analysis are presented in eTable 6. Among the 74 associations, that were overlapped between selected and non-selected meta-analyses with adequate data, only three (4.1%) had convincing evidence; the association between any antidepressant before pregnancy and

SSRI/any antidepressant during pregnancy and autism spectrum disorders (ASD).[29, 84, 215] Three more associations (4.1%) were supported by highly suggestive evidence. These included the association between SSRI before pregnancy and autism spectrum disorders and osteoporotic fractures.[57, 137,151, 13] There was suggestive evidence for eight further associations (10.8%) linked to increased risk of adverse health outcomes. For the rest of the associations, there was either weak (n=32 [43.2%]) or no evidence (n=28 [37.8%]; all associations with $p>0.05$). Overall, we found an agreement between the associations that included in the main analysis and those excluded due to overlap.

eTable 6 Sensitivity analysis results of non-selected meta-analyses due to overlap

Author, year	Risk of adverse health outcome	Antidepressant exposure	Number of cases / total population	Number of study estimates	Study design	Effect metrics	Random effects summary estimate (95% CI)	Random effects summary estimate P value	Largest study summary estimate (95% CI)	I^2 (%)	Egger P value	95% prediction interval	Level of evidence
Ng, 2019	Persistent pulmonary hypertension	SSRI during pregnancy	397/ 7470566	9	Cohort, case-control	OR	1.94 (1.37, 2.76)	$2.1x10^{-3}$	0.79 (0.08, 7.84)	88	0.95	0.70, 5.39	Weak
Kaplan, 2017	Autism spectum disorders	Maternal psychiatric disorder without SSRI	100 / 36925	2	Cohort	OR	1.81 (1.44, 2.29)	$6.0x10^{-7}$	2.02 (1.53, 2.66)	20	0.00	NA	Weak
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during preconception period	8040 / 69219	4	Case-control	OR	1.77 (1.49, 2.09)	$3.3x10^{-11}$	1.90 (1.50, 2.40)	0	0.98	1.22, 2.56	Convincing
Rais. 2014	Autism spectum disorders	Antidepressant during pregnancy	5040 / 50187	3	Case-control	OR	1.50 (0.74, 3.03)	0.260	2.18 (1.37, 3.46)	84	0.87	0.00, 7910.38	No association
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during pregnancy	17318 / 889256	7	Cohort, case-control	OR	1.41 (1.12, 1.78)	0.003	1.46 (1.17, 1.82)	63	0.85	0.72, 2.78	Weak
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during pregnancy	4849 / 772331	2	Cohort	HR	1.26 (0.91, 1.74)	0.160	1.46 (1.17, 1.82)	67	0.00	NA	No association
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during pregnancy	12469 / 116925	5	Case-control	OR	1.52 (1.09, 2.13)	0.014	1.9 (1.48, 2.44)	61	0.61	0.52, 4.44	Weak
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during the first trimester	17318 / 889256	7	Cohort, case-control	OR	1.55 (1.19, 2.03)	0.001	1.46 (1.17, 1.82)	68	0.78	0.70, 3.44	Weak
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during the first trimester	4849 / 772331	2	Cohort	HR	1.26 (0.91, 1.74)	0.161	1.46 (1.17, 1.82)	67	0.00	NA	No association
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during the first trimester	12469 / 116925	5	Case-control	OR	1.79 (1.27, 2.52)	$1.0x10^{-3}$	2.05 (1.58, 2.66)	55	0.76	0.62, 5.13	Suggestive

Mezzacappa, 2017	Autism spectum disorders	Antidepressant during the second trimester	8040 / 69219	4	Case-control	OR	1.67 (1.14, 2.45)	0.009	2.30 (1.63, 3.24)	38	0.38	0.44, 6.33	Weak
Mezzacappa, 2017	Autism spectum disorders	Antidepressant during the third trimester	8040 / 69219	4	Case-control	OR	1.54 (0.82, 2.90)	0.180	2.69 (1.81, 4.00)	73	0.55	0.11, 22.57	No association
Kaplan, 2016	Autism spectum disorders	Non-SSRI antidepressant during pregnancy	3354 / 25728	3	Case-control	OR	2.05 (1.20, 3.49)	0.008	1.93 (0.88, 4.24)	0	0.89	0.07, 64.16	Weak
Kaplan, 2017	Autism spectum disorders	SSRI discontinuation until 3 months before pregnancy vs. unexposed	3852 / 652201	2	Cohort	RR	1.31 (0.98, 1.74)	0.065	1.46 (1.17, 1.82)	46	0.00	NA	No association
Kaplan, 2016	Autism spectum disorders	SSRI during preconception period	6890 / 64569	3	Case-control	OR	1.84 (1.48, 2.28)	$2.4x10^{-8}$	1.90 (1.50, 2.40)	0	0.78	0.46, 7.35	Highly suggestive
Man, 2015	Autism spectum disorders	SSRI during pregnancy	10424 / 107688	4	Case-control	OR	1.81 (1.47, 2.24)	$3.3x10^{-8}$	1.80 (1.40, 2.31)	0	0.94	1.14, 2.88	Convincing
Kobayashi, 2016	Autism spectum disorders	SSRI during pregnancy	10664 / 988245	7	Cohort, case-control	OR	1.45 (1.15, 1.81)	0.002	1.20 (0.90, 1.60)	31	0.18	0.86, 2.43	Weak
Kobayashi, 2016	Autism spectum disorders	SSRI during pregnancy	4068 / 632851	2	Cohort	OR	1.69 (0.80, 3.56)	0.170	1.20 (0.90, 1.60)	82	0.00	NA	No association
Kobayashi, 2016	Autism spectum disorders	SSRI during pregnancy	6596 / 355394	5	Case-control	OR	1.38 (1.08, 1.75)	0.009	1.35 (0.94, 1.93)	0	0.38	0.93, 2.03	Weak
Kaplan, 2016	Autism spectum disorders	SSRI during pregnancy	9061 / 83905	5	Case-control	OR	1.65 (1.23, 2.23)	$1.0x10^{-3}$	1.90 (1.47, 2.45)	38	0.76	0.73, 3.73	Suggestive
Brown, 2017	Autism spectum disorders	SSRI during pregnancy	8695 / 798967	6	Cohort, case-control	OR	1.44 (1.12, 1.85)	0.005	1.20 (0.90, 1.60)	24	0.19	0.82, 2.52	Weak
Brown, 2017	Autism spectum disorders	SSRI during pregnancy	4849 / 772427	2	Cohort	RR	1.54 (0.86, 2.75)	0.153	1.20 (0.90, 1.60)	70	0.00	NA	No association
Brown, 2017	Autism spectum disorders	SSRI during pregnancy	3846 / 26540	4	Case-control	OR	1.44 (1.02, 2.02)	0.037	1.00 (0.59, 1.68)	7	0.37	0.62, 3.35	Weak

Kaplan, 2017	Autism spectum disorders	SSRI during pregnancy	3992 / 679410	3	Cohort	HR	1.61 (1.16, 2.25)	0.005	1.40 (1.02, 1.92)	46	0.33	0.06, 44.64	Weak
Kaplan, 2016	Autism spectum disorders	SSRI during the first trimester	7382 / 65381	4	Case-control	OR	1.91 (1.28, 2.83)	0.001	2.00 (1.54, 2.60)	42	0.98	0.46, 7.91	Weak
Brown, 2017	Autism spectum disorders	SSRI during the first trimester	3846 / 26540	4	Case-control	OR	1.75 (1.16, 2.63)	0.007	1.30 (0.72, 2.36)	21	0.64	0.51, 5.95	Weak
Kaplan, 2016	Autism spectum disorders	SSRI during the second trimester	7382 / 65381	4	Case-control	OR	1.73 (1.15, 2.61)	0.008	2.30 (1.63, 3.25)	29	0.28	0.46, 6.58	Weak
Kaplan, 2016	Autism spectum disorders	SSRI during the third trimester	7382 / 65381	4	Case-control	OR	1.64 (0.83, 3.24)	0.163	2.70 (1.81, 4.03)	68	0.56	0.10, 26.8	No association
Wang, 2015	Risk of Heart Defects	SSRI during pregnancy	NR/ 2010180	4	Cohort	OR	1.22 (0.89,1.67)	0.210	1.60 (1.10, 1.30)	92	0.50	0.31, 4.88	No association
McDonagh, 2014	Preterm birth	Antidepressant during pregnancy	NR / 304	2	Cohort, case-control	OR	1.84 (0.79, 4.27)	0.155	1.73 (0.63, 4.58)	0	NA	NA	No association
Anglin, 2014	Upper gastrointestinal bleeding	SSRIs + or NSAIDs (Patients with various disorders with a diagnosis of upper gastrointestinal bleeding)	85628/ 1020230	19	Cohort, case-control	OR	1.66 (1.44,1.91)	$8.2x10^{-13}$	1.06 (0.57, 1.97)	82	0.80	0.93, 2.95	Suggestive
Painfully, 2013	Cardiovascular malformations	Paroxetine during first trimester	23746/ 1473816	11	Cohort	RR	1.25 (1.01, 1.54)	0.041	1.03 (0.80, 1.33)	30	0.95	0.78, 2.01	Weak
Grigoriadis, 2013	Major malformations	SSRI during first trimester	NR/ 789337	12	Cohort, case-control	RR	0.93 (0.85, 1.02)	0.121	0.78 (0.45, 1.36)	0	0.26	0.83, 1.03	No association
Grigoriadis, 2013	Cardiovascular malformations	SSRI during first trimester	NR/ 345203	13	Cohort, case-control	RR	1.36 (1.08, 1.71)	0.009	0.50 (0.06, 4.43)	31	0.34	0.81, 2.29	Weak
Wu, 2012	Fracture risk	SSRI exposure in general population of older adults	66050/ 385515	12	Cohort, case-control	RR	1.72 (1.51, 1.95)	$4.3x10^{-18}$	1.40 (1.34, 1.46)	91	0.06	1.12, 2.61	Highly suggestive
Eom, 2012	Fracture risk	SSRI exposure in general population of older adults	201627/ 916152	12	Cohort, case-control	RR	1.69 (1.51, 1.90)	$2.5x10^{-19}$	1.40 (1.34, 1.46)	90	0.05	1.14, 2.52	Highly suggestive

Loke, 2008	Upper gastrointestinal bleeding	SSRIs (Patients with various disorders with a diagnosis of upper gastrointestinal bleeding)	2121/ 127048	4	Cohort, case-control	OR	2.35 (1.44, 3.85)	0.001	3.60 (2.70, 4.70)	96	0.43	0.23, 24.66	Weak
Loke, 2008	Upper gastrointestinal bleeding	SSRIs + NSAIDs (Patients with various disorders with a diagnosis of upper gastrointestinal bleeding)	619/ 127048	4	Cohort, case-control	OR	6.33 (3.39,11.81)	6.5x10-9	12.20 (7.10, 19.50)	91	0.16	0.36, 111.44	Weak
Bar-Oz, 2007	Cardiovascular malformations	First trimester paroxetine exposure in pregnancy	188/ 16501	6	Cohort, case-control	OR	1.79 (1.27, 2.53)	0.001	2.16 (1.25, 3.72)	0	0.79	1.10, 2.92	Weak
Bar-Oz, 2007	Major malformations	First trimester paroxetine exposure in pregnancy	646/ 16880	7	Cohort, case-control	OR	1.33 (1.03, 1.71)	0.03	1.83 (0.59, 5.64)	23	0.98	0.78, 2.26	Weak
Rahimi, 2006	Major malformations	SSRI during pregnancy,	97/ 2529	9	Cohort	OR	1.40 (0.86, 2.33)	0.17	1.12 (0.08, 17.78)	0	0.87	0.76, 2.34	No association
Rahimi, 2006	Cardiovascular malformations	SSRI during pregnancy,	21/ 1753	8	Cohort	OR	1.18 (0.36, 3.89)	0.78	3.40 (0.21, 251.89)	0	0.43	0.25, 5.65	No association
Rahimi, 2006	Minor malformations	SSRI during pregnancy	88/ 500	2	Cohort	OR	0.93 (0.13, 6.60)	0.94	0.39 (0.22, 0.71)	0	NA	NA	No association
Rahimi, 2006	Spontaneous abortion	SSRI during pregnancy	225/ 2378	5	Cohort	OR	1.70 (1.26, 2.30)	0,001	2.06 (0.86, 5.17)	0	0.92	1.04, 2.78	Weak
Healy, 2016	Autistic Spectrum or related disorders	SSRI during pregnancy	735/ 83750	5	Case-control	OR	1.99 (1.67, 2.36)	$5.0x10^{-15}$	2.3 (1.23, 2.74)	0	0.57	1.50, 2.63	Weak
Oh, 2014	Risk of coronary heart disease	SSRI	84709/ 925749	12	Cohort, case-control	OR	0.93 (0.65, 1.33)	0.672	1.29 (0.89, 1.87)	98	0.400	0.24, 3.60	No association
McDonagh, 2014	Preterm birth	Antidepressant during pregnancy	NR / 304	2	Cohort, case-control	OR	1.84 (0.79, 4.27)	0.155	1.73 (0.63, 4.58)	0	NA	NA	No association
Huybrechts, 2014	Preterm birth	Antidepressant during early pregnancy (unadjusted)	NR/ 308762	8	Cohort, case-control	OR	1.58 (1.31,1.92)	$2.0x10^{-5}$	1.38 (0.91, 2.10)	14	0.22	1.12, 2.23	Weak

Huybrechts, 2014	Preterm birth	Antidepressant during pregnancy (any time unadjusted)	NR/ 1559757	4	Cohort, case-control	OR	1.44 (1.37, 1.51)	$6.0x10^{-50}$	1.44 (1.37, 1.51)	0	0.50	1.30, 1.61	Suggestive
Huybrechts, 2014	Preterm birth	Antidepressant during pregnancy (any time adjusted)	NR/ 294792	17	Cohort, case-control	OR	1.57 (1.41, 1.75)	$3.x10^{-16}$	1.21 (0.67, 2.21)	19	0.00	1.26, 1.97	Suggestive
Myles, 2013	Major malformations	Fluoxetine during first trimester	NR/ NR	9	Cohort, case-control	OR	1.14 (1.01, 1.30)	0.04	0.79 (0.56, 1.12)	32	0.58	0.76, 1.78	Weak
Myles, 2013	Major malformations	Paroxetine during first trimester	NR/ NR	8	Cohort, case-control	OR	1.29 (1.11, 1.49)	0.001	1.00 (0.06, 16.85)	0	0.28	1.07, 1.55	Weak
Myles, 2013	Major malformations	Sertraline during first trimester	NR/ NR	6	Cohort, case-control	OR	1.01 (0.88, 1.17)	0.88	0.62 (0.09, 4.00)	0	0.84	0.83, 1.24	No association
Myles, 2013	Major malformations	SRI during first trimester	NR/ NR	6	Cohort, case-control	OR	1.06 (0.93, 1.21)	0.37	0.97 (0.81, 1.16)	0	0.59	0.88, 1.28	No association
Myles, 2013	Cardiovascular malformations	Fluoxetine during first trimester	NR/ NR	6	Cohort, case-control	OR	1.21 (0.99, 1.48)	0.07	0.77 (0.19, 3.11)	0	0.57	0.91, 1.61	No association
Myles, 2013	Cardiovascular malformations	Paroxetine during first trimester	NR/ NR	8	Cohort, case-control	OR	1.44 (1.16, 1.79)	0.001	0.88 (0.21, 0.80)	6	0.88	1.03, 2.01	Weak
Myles, 2013	Cardiovascular malformations	Sertraline during first trimester	NR/ NR	8	Cohort, case-control	OR	0.97 (0.64, 1.48)	0.90	0.65 (0.34, 1.25)	63	0.34	0.25, 3.87	No association
Myles, 2013	Minor malformations	SSRI during first trimester	NR/ NR	7	Cohort, case-control	OR	1.18 (0.84, 1.66)	0.34	0.62 (0.20, 1.92)	32	0.33	0.54, 2.59	No association

Nikfar, 2012	Cardiovascular malformations	SSRI during pregnancy,	25128/ 2309472	19	Cohort	OR	1.17 (0.44, 3.09)	0.75	2.17 (0.92, 4.35)	98	0.41	0.02, 70.99	No association
Nikfar, 2012	Minor malformations	SSRI during pregnancy,	2435/ 698770	6	Cohort	OR	1.35 (0.61, 3.00)	0.45	1.06 (0.70, 1.56)	89	0.78	0.10, 18.31	No association
Biffi, 2017	Acute heart disease	TCAs	71838/ 741948	9	Cohort, case-control	RR	1.29 (1.09, 1.54)	0.00	1.41 (1.37, 1.45)	73	0.47	0.81, 2.07	Weak
Biffi, 2017	Haemorrhagic stroke	SSRI	1054/ 159014	3	Cohort, case-control	RR	1.33 (0.86, 2.06)	0.20	1.00 (0.61, 1.63)	38	0.43	0.02, 85.96	No association
Biffi, 2017	Ischaemic stroke	SSRI	4281/ 159014	3	Cohort, case-control	RR	1.15 (0.98, 1.36)	0.09	1.10 (0.88, 1.37)	0	0.37	0.39, 3.37	No association
Zhang, 2017	Atrial septal defect	SSRI during pregnancy	4096/ 2041138	6	Cohort	RR	2.06 (1.40, 3.03)	$2.3x10^{-4}$	2.60 (1.84, 3.68)	58	0.79	0.67, 6.28	Suggestive
Zhang, 2017	Ventricular septal defect	SSRI during pregnancy	12563/ 2990642	7	Cohort	RR	1.15 (0.97, 1.36)	0.11	1.20 (1.04, 1.39)	30	0.11	0.78, 1.68	No association
Ross, 2013	Spontaneous abortion	SSRI during pregnancy	367/ 5780	3	Cohort	RR	1.46 (0.99, 2.16)	0.06	1.48 (0.83, 2.66)	0	0.75	0.12, 18.58	No association
Gao, 2017	Major congenital malformations	Fluoxetine during pregnancy	132646/ 4234692	12	Cohort	RR	1.18 (1.08,1.29	$3.5x10^{-4}$	1.25 (1.10, 1.42)	0	0.49	1.06, 1.30	Suggestive
Gao, 2017	Cardiovascular malformations	Fluoxetine during pregnancy	64921/ 6385820	12	Cohort	RR	1.36 (1.17, 1.59)	$9.0x10^{-5}$	1.34 (1.10, 1.63)	23	0.12	0.99, 1.87	Suggestive
Morales, 2018	Autism spectum disorders	Antidepressant during pregnancy	28105 / 2519942	11	Cohort, case-control	RR	1.53 (1.31, 1.78)	$4.0x10^{-8}$	2.17 (1.20, 3.93)	33	0.82	1.07, 2.19	Convincing
Morales, 2018	Attention deficit hyperactivity disorder	Antidepressant during pregnancy	NR/ NR	7	Cohort, case-control	RR	1.38 (1.13, 1.69)	0.002	0.97 (0.54, 1.73)	53	0.74	0.80, 2.23	Weak
Morales, 2018	Attention deficit hyperactivity disorder	Antidepressant during preconception period	NR/ NR	5	Cohort, case-control	RR	1.38 (1.14, 1.69)	0.001	1.50 (1.01, 2.22)	25	0.96	0.86, 2.24	Weak

Morales, 2018	Attention deficit hyperactivity disorder	Antidepressant during pregnancy	NR/ NR	3	Sibling study design	RR	0.88 (0.70, 1.12)	0.296	0.70 (0.37, 1.31)	0	0.08	0.19, 4.00	No association
Gao, 2018	Major congenital malformations	SSRI during pregnancy	NR/ NR	9	Cohort	RR	1.11 (1.03, 1.19)	0.004	1.13 (1.06, 1.20)	38	0.83	0.94, 1.31	Weak
Gao, 2018	Cardiovascular malformations	SSRI during pregnancy	NR/ NR	18	Cohort	RR	1.24 (1.11, 1.37)	$6.2x10^{-5}$	1.03 (0.86, 1.24)	59	0.45	0.89, 1.71	Weak

TCAs– tricyclic antidepressants, SSRI – selective serotonin reuptake inhibitors, I^2 –heterogeneity, CI – confidence interval, OR – odds ratio, RR – relative risk, HR– hazard ratio, NA– not applicable.

eTable 7 List of covariates used for the sensitivity analysis limited to studies adjusted for covariates

Meta-analysis author, year, outcome	Primary study author year	Factors considered during adjusted analysis
Man, 2018 Attention deficit hyperactivity disorder	Boukhris, 2017	Gender, birth year, maternal age, maternal education level, recipient of social assistance, area of residence, maternal psychiatric disorders in the year prior to or during pregnancy (depression/anxiety, other psychiatric disorders), maternal comorbidities (gestational diabetes, gestational hypertension), maternal history of ADHD
	Laugesen, 2013	Gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy) and maternal anxiolytics/ hypnotics/sedatives use during pregnancy
	Malm, 2016	Sex; socioeconomic status; smoking during pregnancy; neonatal care unit; maternal history of other psychiatric diagnosis; maternal history of substance abuse; paternal history of psychiatric diagnosis; parental death
	Man, 2017	Maternal age at delivery, infant's sex, birth year, birth hospital, parity, maternal underlying medical conditions before delivery (pre-existing diabetes, epilepsy, gestational diabetes, psychiatric conditions, hypertension), use of other psychotropic drugs (antipsychotics, British National Formulary chapter 4.2.1, 4.2.2), and socioeconomic status.
	Sujan, 2017	Parity; year of birth; country of birth; age at childbearing; highest level of completed education; history of any criminal conviction; history of severe psychiatric illnesses (inpatient diagnosis of ICD-8, ICD-9, or ICD-10 schizophrenia, bipolar disorder, or other non-drug-induced psychoses); and history of any suicide attempts.
	Clements, 2015	Gender, race, birth year, insurance type, median income tertile, past history of maternal depression
	Figueroa, 2010	Maternal age group, gender of the child, urban or rural metropolitan statistical area, year of birth, age at last claim and at end of eligibility, maternal and paternal mental health diagnoses, the presence or absence of maternal mental health-related visits by period of time, the use of other psychotropics during pregnancy, and perinatal complications
Fu, 2018 Cataract risk	Becker, 2017	Calendar time (same index date), age, sex, general practice, and number of years of active history in the CPRD before the index date, BMI, smoking, diabetes, hypertension, and systemic steroids
	Chou, 2017	Age, sex, index date, patient's demographics, mental illness characteristics, propensity score derived from comorbid conditions, and concomitant medications
	Klein, 2001	Age and gender
Morales, 2018 Autism pre-pregnancy exposure	Boukhris, 2016	Gender, year of birth, maternal age, marital status, living alone, education, social assistance or care, maternal psychiatric history, paternal psychiatric history, maternal physical history, paternal physical history
	Brown, 2017	Gender, gestational age at delivery, maternal age, maternal psychiatric history, maternal physical history, pre-pregnancy related/delivery, severity of depression, parity, drugs other than antidepressants
	Castro, 2016	Gender, year of birth, gestational age at delivery, maternal age, education, maternal psychiatric history, maternal physical history, severity of depression, parity, insurance type ethnicity or country of origin, maternal income

	Clements, 2015	Gender, year of birth, birth weight, gestational age at delivery, maternal age, education, maternal psychiatric history, maternal physical history, pre-pregnancy related/delivery, severity of depression, parity, insurance type ethnicity or country of origin
	Croen, 2011	Gender, year of birth, birth weight, gestational age at delivery, maternal age, education, maternal psychiatric history, parity, ethnicity or country of origin
	Hviid, 2013	Gender, year of birth, gestational age at delivery, maternal age, education, maternal psychiatric history, smoking status, parity, ethnicity or country of origin residence, employment status
	Sujan, 2017	Year of birth, maternal age, education, maternal psychiatric history, parity, ethnicity or country of origin,
Laporte, 2017 Severe bleeding at any site	de Abajo 1999	UGIB history, smoking status, current use of NSAID, AC, corticosteroids, aspirin
	de Abajo 2000	Hypertension, migraine, asthma or COPD, smoking status, BMI, current use of NSAIDs
	Bak 2002	Age, sex, hypertension, diabetes, smoking status, AC, antiarrhythmics, antianginal drugs
	Meijier 2004	Bleeding history, NSAIDs, AC, glucocorticoids, estrogens, progesterones, histamine blockers, PPIs, antidiabetic agents
	Kurdyak 2005	UGIB history, current use of aspirin, NSAID, glucocorticoid, PPIs, H2 reuptake inhibitors
	Tata 2005	NR
	Helin-Salmivaara 2007	Histamine-2 receptor antagonist, plain misoprostol, PPIs, warfarin, clopidogrel or inhaled glucocorticoid and tramadol, hospitalisation for arthroplasty, hypertension, angina pectoris, cardiac insufficiency, diabetes mellitus, rheumatoid arthritis, asthma
	Kharof 2007	NR
	Vonbach 2007	Glucocorticoids, NSAIDs, AC, SSRIs, TAIs, PPIs, hypertensive disease
	Ziegelstein 2007	NR
	de Abajo 2008	Age, sex, calendar year, smoking status, alcohol intake, history of GI disorder, NSAIDs, systemic corticosteroids, warfarin, low-dose aspirin, antiplatelet drug
	Lewis 2008	Age, sex, race, alcohol consumption, history of ulcer disease, hypertension, PPI use, H2RA use, ASA dose and NSAID dose
	Opatrny 2008	Age, sex, BMI, blood pressure, smoking status, comorbid conditions, warfarin, clopidogrel, antidepressant
	Salkeld 2008	Previous PPH, multiple pregnancy, prolonged labor, abnormalities of the forces of labor, obstructed labor, perineal laceration or other gynecologic laceration, other obstetric trauma, placenta previa, placental abruption, and hypertensive disorders of pregnancy
	Schalekamp 2008	NR
	Vidal 2008	History of peptic ulcer, dyspepsia, UGIB, diabetes mellitus, smoking habit, alcohol consumption and use of antacids, PPIs, sucrafalte, nitrates, systemic NSAIDs, topical NSAIDs, analgesics, antiplatelet drugs, dihidropyridine calcium antagonists and statin
	Barbui 2009	Age, gender, use of antianemic preparations, use of drugs for peptic ulcer

	Chen 2009	Use of aspirin, AC, risperidone, anxiety, alcohol abuse, substance abuse, hypertension, diabetes, hypercholesterolemia, cardiac diseases
	Dall 2009	Age, gender, calendar year, low dose aspirin, PPIs, NSAIDs, alcohol abuse, cerebral ischemia, stroke, warfarin, clopidogrel, dipyridamol, steroids, helicobacter eradication, peptic ulcer, UGIB, cirrhosis
	Targownik 2009	Cardiovascular disease, respiratory disease, hepatic disease, renal disease, active malignancy, alcohol abuse, depression, schizophrenia, acute hospitalisation, upper endoscopy, H2-receptor antagonists, warfarin, clopidogrel, systemic corticosteroids, tricyclic antidepressants
	Carvajal 2011	Alcohol and caffeine consumption, past history of GI disorders, family history of GI bleeding, osteoarthritis, number of medicines taken and use of NSAIDs, salicylates, PPIs, H2 antihistamines, antacids, antiplatelet agents and AC
	Douglas 2011	Smoking, alcohol, BMI, prior history of transient ischemic attack or other stroke, hypertension, diabetes, NSAID use, aspirin use, clopidogrel or dipyridamole use, year of first prescription, observation time
	Verdel 2011	NSAIDs, oral glucocorticoids, PPI, platelet aggregation inhibitors
	de Abajo 2013	Age, gender, calendar year, smoking, peptic ulcer history, number of GP visits in the year prior to index date and concomitant use of other medications
	Andreasen 2006	Age, sex, preoperative use of platelet inhibitors, NSAIDs, oral anticoagulant, place of surgery, use of extracorporal circulation, concomitant valve surgery, Charlson comorbidity index
	Hauta-Aho 2009	Age, sex, study ward, PPI and oral glucocorticoid medications
	Kim 2009	NR
	Gärtner 2010	Age
	Tully 2012	Propensity score (including age, sex, urgency of surgery, previous myocardial infarction, respiratory disease, left ventricular ejection fraction, diabetes mellitus, renal disease, peripheral vascular disease, cerebrovascular disease, cardiogenic shock, heart failure, hypertension, smoking and OPCAB procedure, statin, antiplatelet, anticoagulants)
	Basile 2013	Age, body weight, surgery type
	Mortensen 2013	Propensity-matched analysis (among 5837 users and 30338 non-users) and use of other drugs during follow-up (non-SSRI, other antidepressant, blood pressure lowering drugs, platelet inhibitors, VKA, statins)
	Seitz 2013	Age, sex, Charlson score, number of medications, residence (long-term care or community)
	Quinn 2013	Time varying ATRIA bleeding risk score, INR value
Jiang, 2016 Postpartum hemorrhage	Salkeld 2008	Previous postpartum hemorrhage, multiple pregnancy, prolonged labor, abnormalities of the forces of labor, obstructed labor, perineal laceration or other gynecologic laceration, other obstetric trauma, placenta previa, placental abruption, and hypertensive disorders of pregnancy
	Palmsten 2013	Delivery year, age, race, multiple pregnancy, diabetes, coagulopathy, number of outpatient mood/anxiety disorder diagnoses, number of inpatient mood/anxiety disorder diagnoses, psychotic disorder, other mental health disorder, pain indication, sleep disorder, anticonvulsant dispensing, benzodiazepine dispensing, aspirin dispensing, heparin dispensing, low molecular weight heparin dispensing, warfarin dispensing, and number of outpatient visits and days in hospital during baseline.
	Lindqvist 2014	Maternal age, parity, BMI, educational level, smoking, coagulation defects, history of previous abortion/miscarriage, placental abruption, placenta previa, and maternal depressive symptoms.

	Lupattelli 2014	Maternal age, marital status, BMI, smoking, placenta previa, bleeding episode in first trimester, and depressive symptoms.
	Grzeskowiak 2015	Delivery year, age, socio-economic status, race, multiple pregnancy, parity, smoking status, alcohol or substance abuse during pregnancy, coagulation defects, asthma, diabetes, hypertension, previous caesarean section, and use of other psychotropic medications
	Joseph 2015	Social assistance, residence urban, previous caesarean, multi-foetal pregnancy, placenta previa/ abruption, polyhydramnios, prolonged labour, preeclampsia/eclampsia, epidural analgesia, labour induction, uterine rupture, cervical laceration, caesarean delivery, perineal laceration, vaginal laceration, chorioamnionitis.
	Hanley 2016	Year of birth, maternal age, parity, preterm birth, multifetal pregnancy, diabetes (both gestational and pre-existing), coagulopathy, smoking during pregnancy, blood thinner use in the month before delivery, anxiolytic use in the month before delivery, antipsychotic use in the month before delivery, a diagnosis of mood disorder, any psychiatric visits, or any psychiatric hospitalization in the 5 months before delivery.
	Kim 2016	Age, race, education, parity, comorbid anxiety to the SRI exposure variable, and depressive symptoms.
Jiang, 2015 Upper gastrointestinal bleeding	de Abajo 1999	UGIB history, smoking status, current use of NSAID, AC, corticosteroids, aspirin
	Helin-Salmivaara 2007	Histamine-2 receptor antagonist, plain misoprostol, PPIs, warfarin, clopidogrel or inhaled glucocorticoid and tramadol, hospitalisation for arthroplasty, hypertension, angina pectoris, cardiac insufficiency, diabetes mellitus, rheumatoid arthritis, asthma
	de Abajo 2008	Age, sex, calendar year, smoking status, alcohol intake, history of GI disorder, NSAIDs, systemic corticosteroids, warfarin, low-dose aspirin, antiplatelet drug
	Schalekamp 2008	NR
	Opatrny 2008	Age, sex, BMI, blood pressure, smoking status, comorbid conditions, warfarin, clopidogrel, antidepressant
	Lewis 2008	Age, sex, race, alcohol consumption, history of ulcer disease, hypertension, PPI use, H2RA use, ASA dose and NSAID dose
	Vidal 2008	History of peptic ulcer, dyspepsia, UGIB, diabetes mellitus, smoking habit, alcohol consumption and use of antacids, PPIs, sucrafalte, nitrates, systemic NSAIDs, topical NSAIDs, analgesics, antiplatelet drugs, dihidropyridine calcium antagonists and statin
	Barbui 2009	Age, gender, use of antianemic preparations, use of drugs for peptic ulcer
	Targownik 2009	Cardiovascular disease, respiratory disease, hepatic disease, renal disease, active malignancy, alcohol abuse, depression, schizophrenia, acute hospitalisation, upper endoscopy, H2-receptor antagonists, warfarin, clopidogrel, systemic corticosteroids, tricyclic antidepressants
	Dall 2009	Age, gender, calendar year, low dose aspirin, PPIs, NSAIDs, alcohol abuse, cerebral ischemia, stroke, warfarin, clopidogrel, dipyridamol, steroids, helicobacter eradication, peptic ulcer, UGIB, cirrhosis
	Carvajal 2011	Alcohol and caffeine consumption, past history of GI disorders, family history of GI bleeding, osteoarthritis, number of medicine taken and use of NSAIDs, salicylates, PPIs, H2 antihistamines, antacids, antiplatelet agents and AC
	Verdel 2011	NSAIDs, oral glucocorticoids, PPI, platelet aggregation inhibitors
	de Abajo 2013	Age, gender, calendar year, smoking, peptic ulcer history, number of GP visits in the year prior to index date and concomitant use of others medications

	Wang 2014	Concurrent drug use
	Huang 2011	Age, concurrent drug use
Huang, 2014 Preterm birth	Nordeng 2012	Depression
	Yonkers 2012	Depression
	Latendresse 2011	Depression
	Lewis 2010	Depression
	Lennestal 2007	NR
	Suri 2007	Depression
Wu, 2013 Fracture risk, TCAs	Ensrud 2003	Age, health status, use of ≥1 medication, walking for exercise, functional impairment, fall in previous year, cognitive function, weight change, gait speed, inability to rise from chair, femoral neck BMD
	Lewis 2007	Age, BMD
	Ziere 2008	Age, sex, depression during follow-up period, disability category, lower-limb disability
	Diem 2011	Age, health status, IADL, ability to rise from chair, m-MMSE, smoking, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, thiazide use, PPI use, oral steroid use, weight, GDS score, walks for exercise, history of prior fracture, total-hip BMD and history of falls in previous year
	Coupland 2011	Age, sex, depression, deprivation, smoking status, comorbidities (ischemic heart disease, DM, HTN, stroke, cancer, dementia, epilepsy or seizures, PD, hypothyroidism, OCD) and use of other drugs (eg, statins, NSAIDs, antipsychotics, lithium, aspirin, anti-HTN drugs, anticonvulsants, hypnotics, anxiolytics)
	Ray 1987	Sex, race, age, index year, and home status, diagnosis of dementia
	Ray 1991	Age, sex, calendar year, nursing home residence on index date, and for hospitalization and use of specific medications (narcotic analgesics, anti-HTN, and other cardiovascular drugs) in year preceding index date
	Liu 1998	Age, sex, comorbidity (eg, depression, dementia, osteoporosis), previous drug exposure (eg, sedative, tranquilizer, cardiac drug, anti-PD agent, thyroid-replacement drug, anticonvulsant, insulin, glucocorticoid, estrogen, etidronate)
	Hubbard 2003	Age, sex, general practice, duration of available GPRD data, history of falls, and history of prescriptions for hypnotics and antipsychotics
	Vestergaard 2006	Age, sex, psychiatric comorbidity (eg, manic depression, schizophrenia, alcoholism, eating disorder); medication use (eg, anxiolytic, sedative, neuroleptic, corticosteroid, antiepileptic, cardiovascular agent, lithium); hospital stay; prior fracture; income; working, educational, and residential status; Charlson index
	Van den Brand	Age, sex, geographical region, other antidepressant, use of benzodiazepine, antipsychotic, lithium, anti-PD agent, anticonvulsant, oral-inhaled corticosteroid, bronchodilator, HRT, antiarrhythmic, thiazide diuretic, β-blocker, opioids, anticonvulsants, DM drug, ≥2 dispensings of an NSAID, DMARDs, metoclopramide hydrochloride; history of malignant neoplasm, mental disorder, cerebrovascular disease, obstructive airway disease, or IBD
	Verdel 2010	Age; sex; geographical area; calendar time; cancer; cardiovascular disease; cerebrovascular disease; IBD; mental disorder; obstructive airway disease; use of antidiabetic, antiepileptic, anti-PD drug, antipsychotic, benzodiazepine, β-blocker, DMARD, HRT, NSAID, oral glucocorticoid, opioid

Ross, 2013 Apgar score at 5 minutes	Simon et al., 2002	maternal age, year of delivery, lifetime number of antidepressant prescriptions filled or refilled, lifetime history of outpatient psychiatric treatment, lifetime history of inpatient psychiatric treatment, tobacco use, other substance use, race, number of prior births
	Laine et al., 2003	maternal age, gravidity, parity, gestational age, time and mode of delivery
	Zeskind & Stephens, 2004	maternal age (±2 yrs), maternal cigarette use, low socioeconomic status,
	Pearson et al., 2007	age (±5 years), parity, tobacco use, marital status
	Calderon-Margalit et al., 2009	maternal age, race, marital status, education, smoking during pregnancy, preeclampsia, parity, singleton pregnancy
	Lund et al., 2009	maternal age, BMI, smoking, a previous pregnancy with prematurity, gestational age, previous birth of a low-birth-weight infant, parity, and coffee and alcohol intake
	Wisner et al., 2009	maternal age, race
	Reis et al., 2010	year of birth, maternal age, parity, smoking, body mass index (BMI)
Oderda, 2012 Hip fracture	van den Brand (2009)	Age sex, medications, comorbidities
	Chang (2008)	Age, sex
	Ensrud (2003)	Age, debilitation, gait speed, femoral neck, bone density
	Hubbard (2003)	History of falls, medications
	Wang (2001)	Age, sex, race, medications, debilitation
	Jacqmin-Gadda (1998)	Age, sex, residence
	Guo (1998)	Comorbidities, medications
	Liu (1998)	Comorbidities, medications
	Johansson (1996)	Sex, comorbidities
	Lichtenstein (1994)	Age, sex, comorbidities
	Cumming (1993)	Age, sex, residence
	Jensen (1991)	Age, sex, debilitation, medications
	Ray (1991)	Age, sex, debilitation, medications
	Ray (1987)	Age, sex, race, residence
Barbui, 2009 Suicide attempt and completion	Olfson 2006	White population, median income, number of per capita physicians pediatricians, child psychiatrists and psychiatrists
	Olfson 2006	Age, sex, race, substance use disorder, recent suicide attempt, treatment with antipsychotic anxiolytic, hypnotic, stimulant and mood stabilizing drugs
	Sondergard 2007	Age, sex, and socioeconomic classification

	Tiihonen 2006	Age, sex, geographical location, number of suicide attempts before the index hospitalization, number of suicide attempts during follow/up, use of multiple antidepressants and number of purchased antidepressants during the previous year
	Gibbons 2007	No
	Valuck 2004	Propensity score and calendar year
Khanassov, 2018 Fracture risk; SSRIs	van den Brand, 2009	Age, sex, geographical region, other than SSRIs antidepressants, benzodiazepines, antipsychotics, lithium, anti-Parkinson drugs, anticonvulsants, corticosteroids, hormone-replacement therapy, disease-modifying antirheumatic drugs, nonsteroidal antiinflammatory drugs, antiarrhythmic, thiazide diuretics, beta-blockers, opiates, metoclopramide, antidiabetic drugs; history of hospitalization
	Verdel, 2010	Age, sex, geographical region, calendar time, other than SSRIs antidepressants, benzodiazepines, antipsychotics, lithium, anti-Parkinson drugs, anticonvulsants, corticosteroids, hormone-replacement therapy, disease-modifying antirheumatic drugs, nonsteroidal antiinflammatory drugs, antiarrhythmic, thiazide diuretics, beta-blockers, opiates, metoclopramide, antidiabetic drugs, thyroid hormones; history of hospitalization
	Vestergaard, 2006	Age, sex, psychiatric comorbidity (eg, schizophrenia, alcoholism), medication use such as anxiolytic, sedative, neuroleptic, corticosteroid, antiepileptic, lithium, hospitalization, prior fracture, income, working status, education, residence, Charlson index
	Bolton, 2008	Age, sex, ethnicity, income, residence, comorbidity index of the John Hopkins Ambulatory Care Group system (diabetes, ischemic heart disease, myocardial infarction, hypertension, epilepsy, rheumatoid arthritis, organ transplantation, COPD, home care use, depression, substance abuse, dementia, schizophrenia), medication use such as anticonvulsants, diuretics, anticoagulant, thyroid hormone
	Liu, 1998	Age, sex, comorbidities (depression, dementia and other), medications such as sedatives, tranquillizers, cardiac agents, anti-Parkinson drugs, thyroid hormones, anticonvulsants, diabetic agents, corticosteroids, estrogens, etidronate; different exposure categories and doses of antidepressant
	Abrahamsen, 2009	Age, previous fracture, modified Charlson comorbidity index, groups of medications
	Wang, 2016	Age, sex, hypertension, diabetes, osteoporosis, history of falls, cardiac diseases, chronic obstructive pulmonary disease, urinary incontinence, Parkinson disease, chronic mental disorders, dementia, depression, liver disease, peripheral vascular disease, cerebrovascular disease, arthritis, chronic kidney diseases, glaucoma; use of medications (opiates, nonopioid analgesics, antipsychotics, anxiolytics, sedatives, corticosteroids, hormone replacement therapy, antiepileptics, tricyclics
	Rabenda, 2012	Lumbar spine, femoral neck and total hip BMD, depression, history of vertebral/ nonvertebral fracture, benzodiazepine use, antihypertensive and antiarrhythmic drugs
	Spangler, 2008	Age, BMD, height, weight, ethnicity, physical function, hormone replacement therapy, smoking, years since menopause, number of falls, previous fracture, use of analgesics, narcotics, cardiovascular diseases
	Richards, 2007	Age, sex, education, study center, BMI, comorbidities based on modified Charlson index, self-reported general health, prior smoking and alcohol intake, history of falls and fractures, calcium and vitamin D intake, dementia based on MMSE, depression, medication use such as bisphosphonates, antihypertensive, diuretics, corticosteroids, estrogens, benzodiazepines, anticonvulsants, antipsychotics, tricyclics, BMD
	Lewis, 2007	Age, BMD
	Schneeweiss, 2004	BMI, current smoking status, activities of daily living, cognitive impairment

	Carriere, 2016	Age, center, sex, smoking, benzodiazepines, other CNS drugs, osteo-articular pain, time since first depressive episode, antiosteoporosis drugs, corticosteroids
	Ensrud, 2003	Age, health status, one or more medical conditions, walking for exercise, functional impairment, fall in previous year, cognitive function, weight change, gait speed, inability to rise from chair, femoral neck bone density.
	Ziere, 2008	Age, sex, disability category, lower limb disability, depression
	Diem, 2011	Age, health status, instrumental daily activities, ability to rise from chair, MMSE, smoking, alcohol use, hormone replacement therapy, bisphosphonate use, benzodiazepine use, thiazide use, proton pomp inhibitor use, corticosteroid use, weight, depression, walks for exercise, prior fracture, BMD
	Coupland, 2011	Age, sex, year of depression diagnosis, diagnosis of depression before age 65, severity of index depression, deprivation level, smoking status, comorbidities (heart conditions, diabetes, dementia, cancer, epilepsy, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, stroke), use of statins, nonsteroidal antiinflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive, anticonvulsants, hypnotics), previous falls.
	Bakken, 2013	Sex, birth year, time period
	Cheng, 2016	Age, sex, urbanization, osteoporosis, Charlson comorbidity index
	Souverein, 2016	Age, sex, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol
	Sheu 2015	Age, sex, previous fracture, corticosteroids, rheumatoid arthritis, smoking, alcohol use, BMI, osteoporosis, history of bone diseases, previous use of bisphosphonates or other bone protecting drugs: raloxifene, strontium ranelate, parathyroid hormone, calcium, vitamin D, calcitonin, calcitriol
	Adachi,2014	Age, BMI, parental history of hip fracture, rheumatoid arthritis, prior fracture, osteoarthritis, celiac disease, Crohn's disease, Parkinson's disease, falls in the past year, smoking, alcohol intake, anxiety, depression, general health, physical function and vitality

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3–4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eBox1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 Supplement methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12-13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 eTable 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2-3, eTables 2-4
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 2-3, eTables 2-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13 Supplement results
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18-19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	6-7
2	Hypothesis statement	7
3	Description of study outcome(s)	7-8
4	Type of exposure or intervention used	7-8
5	Type of study designs used	7-8
6	Study population	7-9
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	NA
8	Search strategy, including time period included in the synthesis and key words	7, eBox1
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	NA
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Figure 1, eTable 1
14	Method of addressing articles published in languages other than English	We placed restrictions on English.
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	8-9
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	8-9
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9-10
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9-10
22	Assessment of heterogeneity	9-10
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9-10
24	Provision of appropriate tables and graphics	Tables 1-4, Figure 1, Supplement file
Reporting of results should include		

25	Graphic summarizing individual study estimates and overall estimate	Tables 2-3, Supplement file
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Table 4, Supplement file
28	Indication of statistical uncertainty of findings	Supplement file

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	NA
30	Justification for exclusion (eg, exclusion of non-English language citations)	NA
31	Assessment of quality of included studies	11, Table 4
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14-17
34	Guidelines for future research	17
35	Disclosure of funding source	18-19

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Supplementary references

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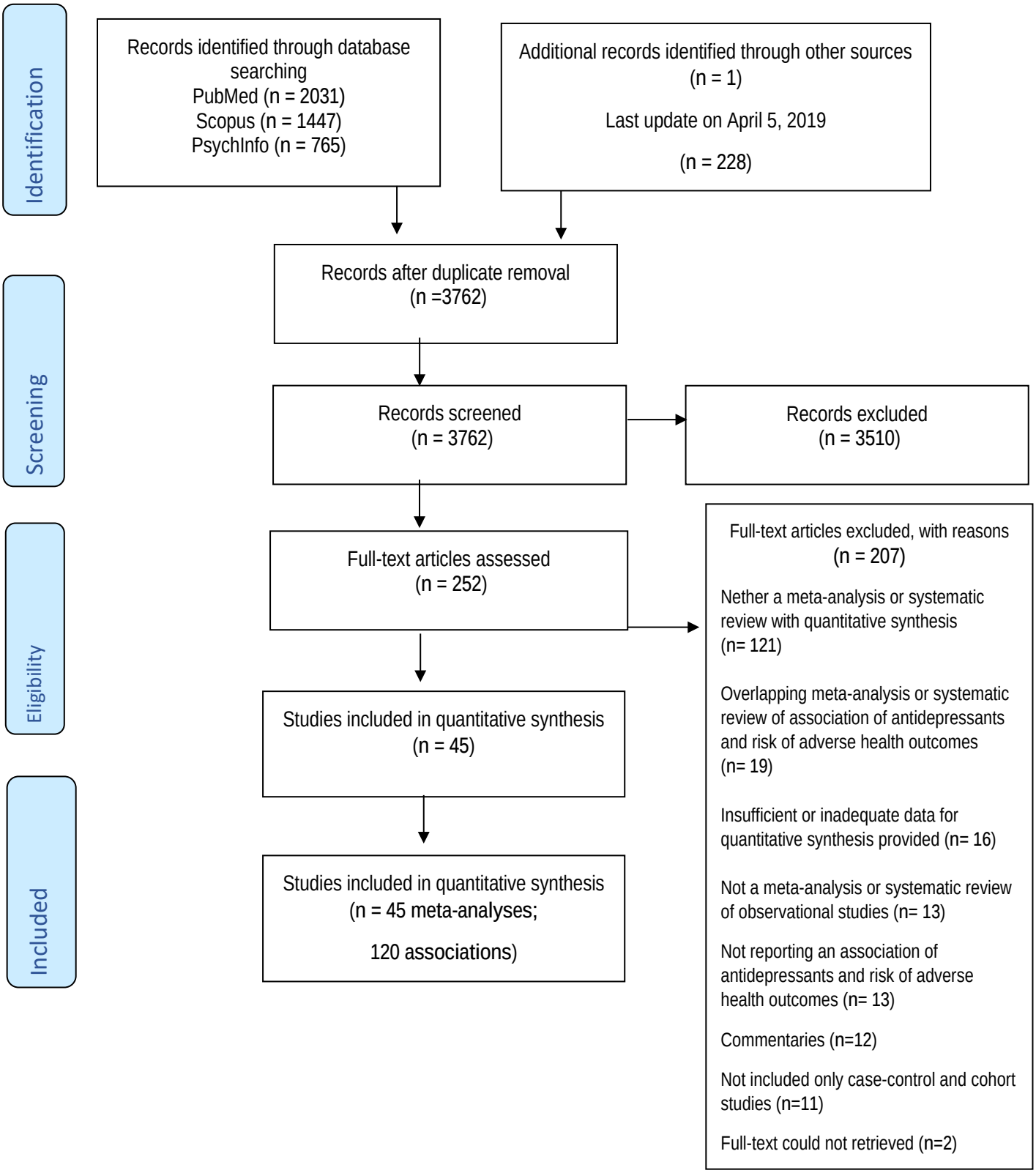

Figure 1 Flowchart outlining the literature search and evaluation process of published meta-analyses and systematic reviews

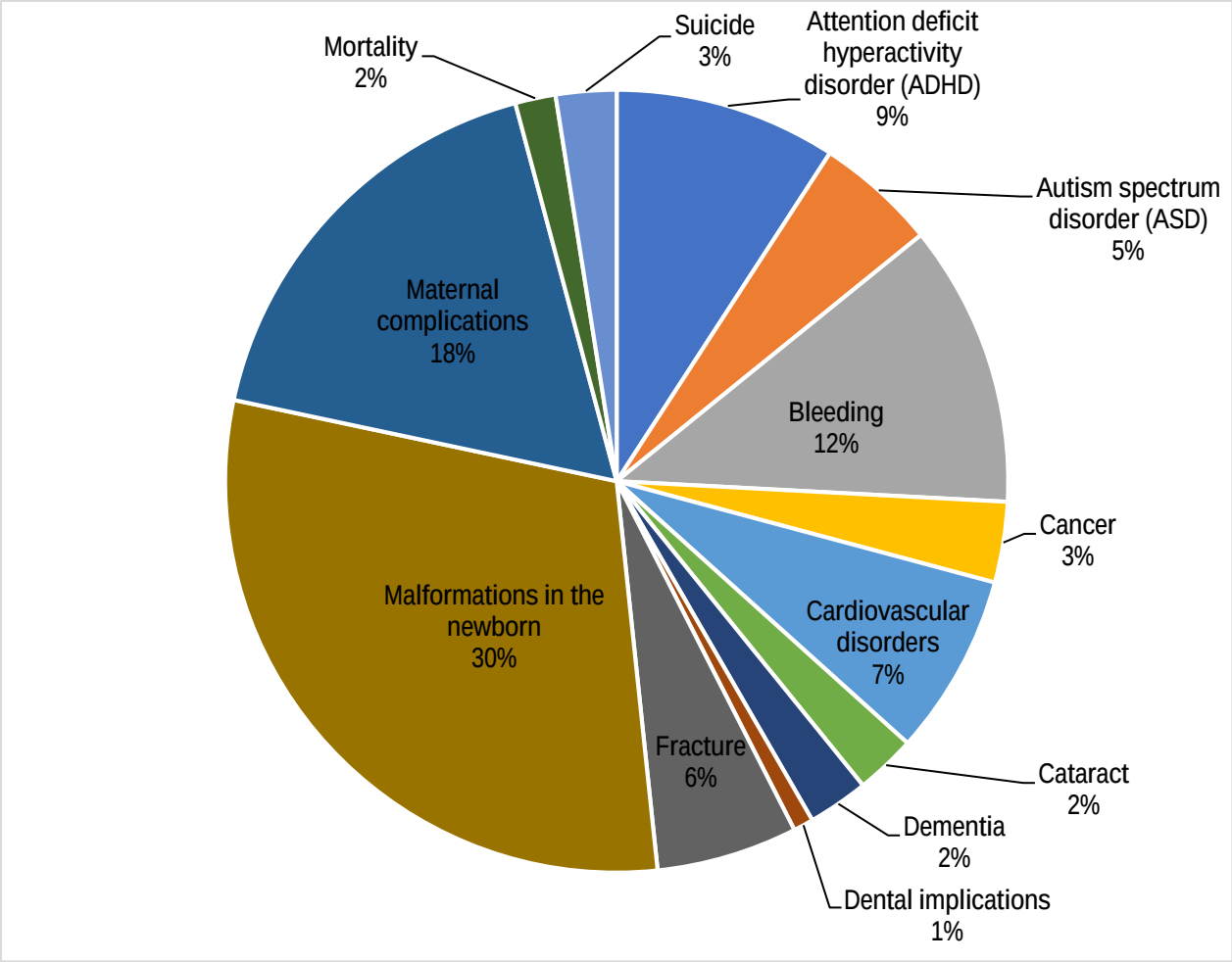

Figure 2. Percentages of the reported 13 adverse health outcomes related to exposure to antidepressants in the published 45 meta-analyses.